Condensation of Reissert Hydrofluoroborate Salts with Alkenes and Alkynes

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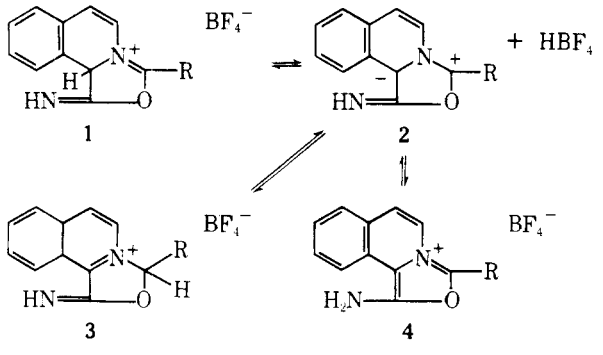
The hydrofluoroborate salts of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds) undergo reactions with alkenes to give substituted 2-(1-isoquinolyl)pyrroles and with alkynes to give substituted pyrrolo[2,1-*a*]isoquinolines. To expand the scope and synthetic usefulness of these reactions, a wide variety of Reissert salts, alkenes, and alkynes, respectively, have been utilized. The reactions are general in nature. They take place successfully when the acyl group of the Reissert compound is varied from a simple aliphatic one (*N*-acetyl, for example) to a sterically hindered aromatic one [*N*-(1-naphthoyl)]. The olefin reactions take place with monosubstituted ethylenes (styrene) and with 1,2-disubstituted ethylenes (*trans*-stilbene). Also, the reactions occur when either electron-withdrawing (as in diethyl maleate) or electron-donating [as in 1-(3,4-dimethoxyphenyl)propene] substituents are bonded to the ethylene moiety. With regard to the alkyne reactions, wide variations in either the Reissert salt or the alkynes are also consonant with successful reactions.

Evidence has been presented that solutions of the hydrofluoroborate salts of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds[4]) consist of equilibrium mixtures of **1**, **3**, and **4**, the latter being the major component.[2,3] These salts

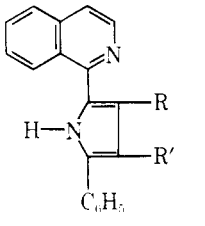


are also presumed to be in equilibrium with the original Reissert compound, the 1,3-dipolar compound **2** (a mesoionic compound), and fluoroboric acid. Several studies of 1,3-dipolar addition reactions of hydrofluoroborate salts of Reissert compounds have been reported.[5-8] Numerous examples of complex, acid-catalyzed condensation–rearrangement reactions of Reissert compounds with olefins have also been reported.[9-13] It is believed that these condensation–rearrangement reactions involve an initial Diels–Alder type of cycloaddition of the olefin to the isomeric form **4** of the Reissert salt, and detailed mechanisms of reaction have been suggested.[11,12]

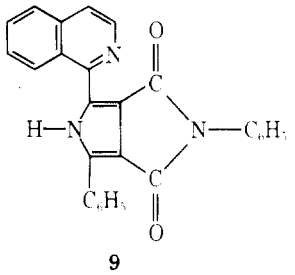
In order to expand the scope and synthetic usefulness of these reactions, we have now carried out reactions of a variety of Reissert hydrofluoroborate salts with a variety of olefinic and acetylenic compounds. The results of the reactions with olefinic compounds are summarized in Table I, and those with acetylenic compounds in Table II. It is clear that both types of reactions are general in nature. The reactions take place successfully when the acyl group of the Reissert compound is varied from a simple aliphatic one (*N*-acetyl, for example) to a sterically hindered aromatic one [*N*-(1-naphthoyl)]. The olefin reactions take place with both monosubstituted ethylenes (styrene) and with 1,2-disubstituted ethylenes (stilbene). Also, the reactions occur when either electron-withdrawing (as in diethyl maleate) or electron-donating [as in 1-(3,4-dimethoxyphenyl)propene] substituents are bonded to the ethylene moiety. It is also clear from the data presented in Table II and in previous publications[5-8] that wide variation in the acetylenes is consonant with successful reactions.

The structures of many of the products listed in Tables I and II have been established in an unambiguous manner. The remaining structural assignments are based on analyses, spectral data, and analogy.

The structure of diethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3,4-dicarboxylate (**8**), obtained by the condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**4**, R = C_6H_5) with diethyl maleate, was established by a decarbethoxylation reaction with refluxing 85% phosphoric acid to give the known compound 2-(1-isoquinolyl)-5-phenylpyrrole (**23**).[12] Similarly, sulfuric acid catalyzed ethanolysis of



8, R = R′ = $CO_2C_2H_5$
23, R = R′ = H
5, R = C_6H_5; R′ = H
16, R = R′ = C_6H_5



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2-(1-isoquinolyl)-3,4-(*N*-phenyldicarboximido)-5-phenylpyrrole (**9**), the product of the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate with *N*-phenylmaleimide, gave a mixture of diethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3,4-dicarboxylate (**8**) and 2-(1-isoquinolyl)-5-phenylpyrrole (**23**).

2-(1-Isoquinolyl)-3,5-diphenylpyrrole (**5**), the product of the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate with styrene, is a known compound.[13] It had been synthesized by an unambiguous method involving a Bischler–Napieralski reaction as the key step. In like manner, 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**16**) is a known compound,[14] and one which has also been synthesized in an unambiguous manner.[9] The product of the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate with *trans*-stilbene was identical with the known compound **16** in every regard (melting point and IR and NMR spectra).

An independent and unambiguous synthesis of 1,2,3-triphenylpyrrolo[2,1-*a*]isoquinoline (**18**) has been achieved by reaction of the lithium salt of 1-benzylisoquinoline with 2-(α-bromobenzyl)-2-phenyl-1,3-dioxolane (the ethylene glycol ketal of desyl bromide) and with subsequent treatment of the reaction mixture with polyphosphoric acid.[5] The IR and NMR

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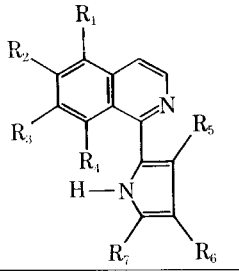
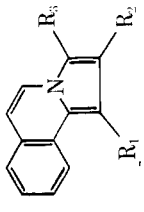
Table I. Reactions of Reissert Hydrofluoroborate Salts with Olefins



1,2-dihydroisoquinaldonitrile	registry no.	olefin	registry no.	product[a] no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	mp, °C	yield, %	conditions
2-benzoyl (1 equiv)	68001-26-3	styrene (2 equiv)	100-42-5	**5**	H	H	H	H	C_6H_5	H	C_6H_5	229–231[b]	66	DMF, 100 °C, 20 h
2-*p*-anisoyl-7,8-dimethoxy (1 equiv)	68001-28-5	styrene (5 equiv)		**6**	H	H	OMe	OMe	C_6H_5	H	*p*-$MeOC_6H_4$	134–135	16	DMF, 100 °C, 20 h
2-*p*-anisoyl-7,8-dimethoxy (1 equiv)		1-(3,4-dimethoxyphenyl)propene (5 equiv)	93-16-3	**7**	H	H	OMe	OMe	3,4-$(MeO)_2$-C_6H_3	Me	*p*-$MeOC_6H_4$	159–160	30	DMF, 100 °C, 20 h
2-benzoyl (1 equiv)		diethyl maleate (5 equiv)	141-05-9	**8**	H	H	H	H	CO_2Et	CO_2Et	C_6H_5	179–180	54	DMF, 150 °C, 50 h
2-benzoyl (1 equiv)		*N*-phenylmaleimide (5 equiv)	941-69-5	**9**[c]								293–294	42	DMF, 150 °C, 50 h
2-*p*-anisoyl-5,6,7-trimethoxy (1 equiv)	68001-30-9	styrene (5 equiv)		**10**	OMe	OMe	OMe	H	C_6H_5	H	*p*-$MeOC_6H_4$	198–200	60	DMF, 100 °C, 24 h
2-*p*-anisoyl-5,6,7-trimethoxy (1 equiv)		1-(3,4-dimethoxyphenyl)propene (5 equiv)		**11**	OMe	OMe	OMe	H	3,4-$(MeO)_2$-C_6H_3	Me	*p*-$MeOC_6H_4$	134–136	13	DMF, 150 °C, 24 h
2-acetyl (1 equiv)	68001-32-1	dimethylmaleate (2 equiv)		**12**	H	H	H	H	CO_2Me	CO_2Me	CH_3	139–140	76	CH_2Cl_2–EtOH, reflux, 2 h
2-isobutyryl (1 equiv)	68001-34-3	dimethylmaleate (2 equiv)		**13**	H	H	H	H	CO_2Me	CO_2Me	$CHMe_2$	165–166	68	CH_2Cl_2–EtOH, reflux, 2 h
2-(cyclopropanecarbonyl) (1 equiv)	68001-36-5	dimethyl maleate (2 equiv)		**14**	H	H	H	H	CO_2Me	CO_2Me	C_3H_5	188–189	70	CH_2Cl_2–EtOH, reflux, 2 h
2-(1-naphthoyl) (1 equiv)	68001-38-7	dimethyl maleate (2 equiv)		**15**	H	H	H	H	CO_2Me	CO_2Me	1-$C_{10}H_7$	117–122	37	CH_2Cl_2–EtOH, DMF, reflux, 2 h
2-benzoyl (1 equiv)		*trans*-stilbene (1 equiv)	103-30-0	**16**	H	H	H	H	C_6H_5	C_6H_5	C_6H_5	268–270[d]	34	DMF, 100 °C, 24 h
2-benzoyl (1 equiv)		*trans*-stilbene (30 equiv)		**16**	H	H	H	H	C_6H_5	C_6H_5	C_6H_5	268–270[d]	60	DMF, 100 °C, 24 h

[a] Products were characterized by elemental analysis, IR, spectra, and NMR spectra. [b] A known compound; reported[11] mp 226–228 °C. [c] See structure **9** in the main text. [d] A known compound; reported[7] mp 263–264 °C.

Table II. Reactions of Reissert Hydrofluoroborate Salts with Alkynes



1,2-dihydro-isoquin-aldonitrile	alkyne	registry no.	product[a] no.	R_1	R_2	R_3	mp, °C	yield, %	conditions
2-benzoyl (1 equiv)	phenylacetylene (2 equiv)	536-74-3	17	C_6H_5	H	C_6H_5	138–140[b]	57	DMF, 120 °C, 24 h
2-benzoyl (1 equiv)	diphenylacetylene (3 equiv)	501-65-5	18	C_6H_5	C_6H_5	C_6H_5	178–179	28	DMF, reflux, 24 h
2-acetyl (1 equiv)	dimethyl acetylenedicarboxylate (3 equiv)	762-42-5	19	CO_2Me	CO_2Me	CH_3	175–176	64	DMF, 100 °C, 22 h
2-isobutyryl (1 equiv)	dimethyl acetylenedicarboxylate (3 equiv)		20	CO_2Me	CO_2Me	$CHMe_2$	111–112	26	DMF, 100 °C, 22 h
2-(cyclopropane carbonyl) (1 equiv)	dimethyl acetylenedicarboxylate (3 equiv)		21	CO_2Me	CO_2Me	C_3H_5	131–132	47	DMF, 100°C, 22 h
2-(1-naphthoyl) (1 equiv)	dimethyl acetylenedicarboxylate (3 equiv)		22	CO_2Me	CO_2Me	1-$C_{10}H_7$	196–197	40	DMF, 100 °C, 22 h

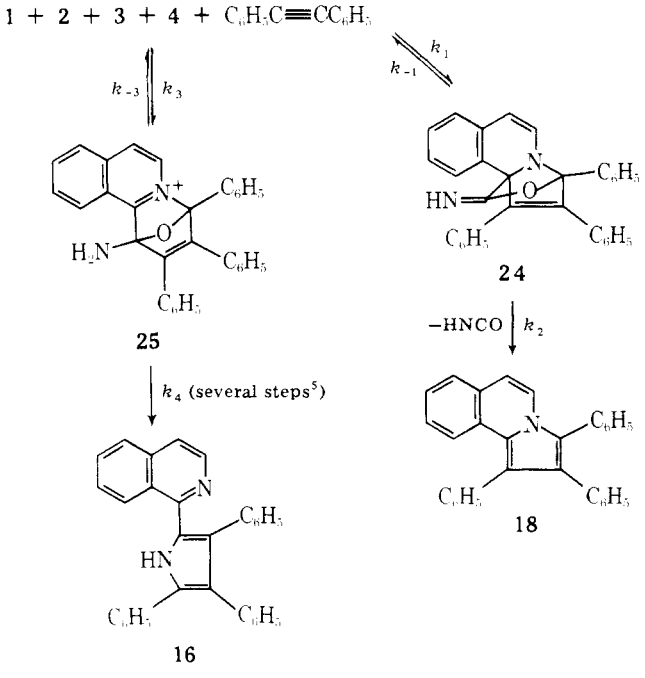
[a] Products were characterized by elemental analysis, IR spectra, and NMR spectra. [b] A known compound; reported[5] mp 136–138 °C.

spectra of the authentic sample were identical with those of the product of the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate with diphenylacetylene (tolan), and a mixture melting point test of the two samples showed no depression.

A small amount of 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**16**) was formed together with the major product 1,2,3-triphenylpyrrolo[2,1-*a*]isoquinoline (**18**) in the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate with diphenylacetylene. It was shown conclusively, by means of control experiments, that the former compound arose directly from the diphenylacetylene reaction and was not attributable to the presence of a small amount of stilbene, as an impurity, in the diphenylacetylene.

As suggested previously,[5] the mechanism for the formation of 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**16**) from **4** (R = C_6H_5) and *trans*-stilbene involves an initial Diels–Alder reaction. A mechanism has also been proposed[5] for the formation of **16**, as a minor product, in the reaction of **4** (R = C_6H_5) with tolan. Furthermore, evidence has been presented[6,7] that the major product, **18**, of the latter reaction arises by way of a 1,3-dipolar cycloaddition reaction.

In light of these and previously reported results, we are able to provide an explanation for the fact that alkenes give substituted 2-(1-isoquinolyl)pyrroles (**5–16**) in reactions with Reissert hydrofluoroborate salts (**4**), while alkynes give predominantly substituted pyrrolo[2,1-*a*]isoquinolines (**17–22**). We have already demonstrated[6] that some of the reactions between **2** and ethyl phenylpropiolate in DMF–ethanol solution at 41 °C are second- and first-order reversible ones, and it is well known that Diels–Alder reactions are reversible. Thus, it is reasonable to assume that the equilibrium mixtures of **1**, **2**, **3**, and **4** can undergo the initial steps of both types of



reaction with either alkenes or alkynes. As an illustration, let us consider the reactions of tolan with 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1–4**, R = C_6H_5).

Since the initial competing cycloaddition reactions are reversible, the predominance of **18** over **16** in the product mixture depends on the relative velocities of the final irreversible steps. Conversion of **24** (involving only loss of HNCO) to a transition species, which, by bond reorganization, can become an aromatic product (**18**), possibly represents an important driving force. Thus, this step is a relatively rapid one. On the other hand, the conversion of **25** to **16** involves several steps,

including the formation of several relatively high energy, unstable intermediates.[5] For this reason, $k_2 > k_4$, and **18** is the major product.

The same argument may be used to explain the fact that Reissert hydrofluoroborate salts react with alkenes exclusively by way of the initial Diels–Alder cycloaddition, even though alkenes are also good 1,3-dipolarophiles. In these cases, only the Diels–Alder pathway allows the eventual formation of stable products by energetically favorable routes.

Some understanding of the difference in yields of products shown in Tables I and II can be gleaned by consideration of the previous discussion. It is well known that the presence of electron-withdrawing substituents increases the rates of ordinary Diels–Alder and 1,3-dipolar cycloaddition reactions, and both are sensitive to steric considerations. In terms of the ideas presented here, this means that the presence of electron-withdrawing substituents and minimization of steric interactions should lead to increased concentrations of intermediates of the types **24** and **25** in the respective equilibrium mixtures. These increased concentrations will, in turn, lead to overall increases in the rates of formation of products. Ordinarily, this will also be reflected in higher yields of products. Much of the data presented in Tables I and II can be accommodated on the basis of these considerations. Also, the increased yields which result when an excess of alkene or alkyne is employed are readily understood on the basis of the initial equilibrium considerations.

Experimental Section

A. Preparation of Reissert Hydrofluoroborate Salts. 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C_6H_5). This compound, mp 196–198 °C dec, was prepared as described previously.[7]

2-*p*-Anisoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile. This compound was prepared from 6.9 g (0.04 mol) of 7,8-dimethoxyisoquinoline[15] by the usual procedure.[7] The product weighed 7.3 g (57%): mp 160–161 °C; IR (KBr) 2940, 2840, 1650, 1600, 1570, 1340, 1180, 1080, 1060, 1020, 880, 760, 730 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (s, 3 H), 3.8 (s, 3 H), 4.0 (s, 3 H), 5.8 (d, 1 H, J = 8.0 Hz), 6.9 (m, 6 H), 7.6 (d, 2 H, J = 8.4 Hz).

Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 7.99. Found: C, 67.92; H, 5.35; N, 7.71.

2-*p*-Anisoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile Hydrofluoroborate. This compound was prepared from 3.0 g (8.6 mmol) of 2-*p*-anisoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile by the usual procedure.[7] The product weighed 1.9 g (51%): mp 199–200 °C; IR (KBr) 3410, 1650, 1590, 1480, 1280, 1260, 1180, 950, 840, 825 cm^{-1}.

Anal. Calcd for $C_{20}H_{19}N_2O_4BF_4$: C, 54.82; H, 4.37; N, 6.39. Found: C, 54.89; H, 4.44; N, 6.28.

2-*p*-Anisoyl-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile. This compound was prepared from 7.8 g (0.04 mol) of 5,6,7-trimethoxyisoquinoline[15] by the usual procedure.[7] The product weighed 12.3 g (91%): mp 153–154 °C; IR ($CHCl_3$) 2940, 2840, 1655, 1600, 1460, 1340, 1250, 1180, 1125, 1030 cm^{-1}; NMR ($CDCl_3$) δ 3.83 (s, 3 H), 3.88 (s, 6 H), 3.93 (s, 3 H), 6.30 (d, 1 H, J = 7.5 Hz), 6.42 (s, 1 H), 6.60 (d, 1 H, J = 7.5 Hz), 6.70 (s, 1 H), 6.90 (d, 2 H, J = 9.0 Hz), 7.60 (d, 2 H, J = 9.0 Hz).

Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.13; H, 5.35; N, 7.32.

2-*p*-Anisoyl-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile Hydrofluoroborate. This compound was prepared from 5.0 g (0.01 mol) of 2-*p*-anisoyl-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile by the usual procedure.[7] The product weighed 5.0 g (81%): mp 164–165 °C; IR (KBr) 3340, 3080, 1650, 1600, 1490, 1290, 1270, 1190, 1125, 1040 cm^{-1}.

Anal. Calcd for $C_{21}H_{21}N_2O_5BF_4$: C, 53.87; H, 4.52; N, 5.98. Found: C, 53.85; H, 4.57; N, 5.97.

2-Acetyl-1,2-dihydroisoquinaldonitrile. This compound was prepared according to the method of Popp and Soto[16] in 84% yield and was recrystallized from absolute ethanol, mp 121.5–122.5 °C (lit.[16] mp 119–121 °C).

2-Acetyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = CH_3). This compound was prepared from 4.38 g (0.022 mol) of 2-acetyl-1,2-dihydroisoquinaldonitrile by the usual procedure.[7] The product weighed 5.74 g (91%): mp 170 °C dec; IR (Nujol) 3450, 3350, 2930, 1680, 1605, 1455, 1370, 1295, 1230, 1080, 800 cm^{-1}; NMR (Me_2SO-d_6) δ 2.85 (s, 3 H), 7.5 (m, 7 H).

2-Isobutyryl-1,2-dihydroisoquinaldonitrile. This compound was prepared according to the method of Popp and Soto[16] in 11% yield and was recrystallized from absolute ethanol, mp 86.5–87.5 °C (lit.[16] mp 87–88 °C).

2-Isobutyryl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = *i*-Pr). This compound was prepared from 2.49 g (0.011 mol) of 2-isobutyryl-1,2-dihydroisoquinaldonitrile by the usual procedure.[7] The product weighed 2.94 g (85%): mp 170.5 °C dec; IR (Nujol) 3300, 2890, 1660, 1625, 1465, 1370, 1310, 1280, 1200, 1060, 800, 760 cm^{-1}; NMR (Me_2SO-d_6) δ 1.6 (d, 6 H, J = 7.2 Hz), 3.8 (m, 1 H), 7.7 (m, 7 H).

2-(Cyclopropanecarbonyl)-1,2-dihydroisoquinaldonitrile. This compound was prepared according to the method of Popp and Soto[16] in 79% yield and was recrystallized from 95% ethanol, mp 111–112 °C (lit.[16] mp 109–111 °C).

2-(Cyclopropanecarbonyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = Cyclopropyl). This compound was prepared from 2.46 g (0.011 mol) of 2-(cyclopropanecarbonyl)-1,2-dihydroisoquinaldonitrile by the usual procedure.[7] The product weighed 3.27 g (95%): mp 178 °C dec; IR (Nujol) 3410, 3320, 3110, 2920, 2850, 1670, 1630, 1610, 1580, 1465, 1420, 1385, 1310, 1275, 1210, 1060, 930, 870, 780, 750 cm^{-1}; NMR (Me_2SO-d_6) δ 1.4 (m, 4 H), 2.6 (m, 1 H), 7.5 (m, 7 H).

2-(1-Naphthoyl)-1,2-dihydroisoquinaldonitrile. This compound was prepared by a modification of the method of Popp and Soto.[16]

After repeated evacuation and flushing of the apparatus with dry nitrogen, a solution of potassium cyanide (15.7 g, 0.24 mol) in 40 mL of water and of isoquinoline (9.8 mL, 0.08 mol, freshly distilled) in 100 mL of methylene chloride was introduced into the flask. To the dropping funnel was added a freshly prepared solution of 1-naphthoyl chloride (30.9 g, 0.16 mol)[17] in 40 mL of methylene chloride. The acid chloride was added to the two-phase mixture during 1 h 40 min at room temperature with moderate stirring and rapid nitrogen flow. The nitrogen stream was then stopped, and stirring was continued for 6 h. The solid which formed was collected by filtration and washed with water and methylene chloride, yielding 3.98 g of the desired product, which was recrystallized from 95% ethanol, mp 204.0–206.5 °C (lit.[16] mp 198–200 °C).

To recover additional compound, the methylene chloride and aqueous layers were separated. The latter was washed well with methylene chloride, and the organic solutions were combined. This resulting organic solution was washed with water, 5% HCl, water, 5% NaOH (until a portion yielded no more naphthoic acid on acidification), and water. During the early washes, a white solid (1.65 g) separated from the two phases. This solid, which was collected and purified, proved to be the desired Reissert compound. The methylene chloride solution was now dried and concentrated. Its residue (28.6 g) was identified as a mixture of the desired Reissert compound and naphthoic anhydride. The former (5.86 g) was recovered from the mixture by fractional crystallization from 95% ethanol. The total yield of 2-(1-naphthoyl)-1,2-dihydroisoquinaldonitrile obtained was 11.49 g (44.5%).

2-(1-Naphthoyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = 1-Naphthyl). This compound was prepared from 0.50 g (1.6×10^{-3} mol) of 2-(1-naphthoyl)-1,2-dihydroisoquinaldonitrile by the usual procedure.[7] The product weighed 0.49 g (76%): mp 214 °C dec; IR (Nujol) 3440, 3320, 2920, 2850, 1660, 1460, 1375, 1210, 1075, 780, 760 cm^{-1}.

B. Reactions of Reissert Hydrofluoroborate Salts with Olefins. Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with Styrene. A mixture of 2.3 g (6.55 mmol) of 4 (R = C_6H_5), 1.5 mL (13.1 mmol) of freshly distilled styrene, and 20 mL of anhydrous *N,N*-dimethylformamide was heated, with stirring, on the steam bath for 20 h. The reaction mixture was poured into 500 mL of water, and the aqueous suspension was extracted with ten 100-mL portions of benzene. The benzene extract was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated almost to dryness. The concentrated solution was chromatographed on neutral alumina (activity I[18]), a benzene–chloroform mixture (1:1) being used as the eluent. The product, 2-(1-isoquinolyl)-3,5-diphenylpyrrole (**5**), was obtained by evaporation of the eluent of the first yellow band. There was obtained 1.5 g (66%) of the compound, mp 229–231 °C (lit.[13] mp 226–228 °C). A mixture melting point with a sample of authentic[13] compound showed no depression, and the IR and NMR spectra of the two samples were identical.

Reaction of 2-*p*-Anisoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with Styrene. The procedure

utilized for the reaction between the Reissert salt **4** (R = C_6H_5) and styrene was used. In this particular condensation, 5 equiv of styrene was employed. The yield of the product (**6**) was 16%: mp 134–135 °C; IR ($CHCl_3$) 3460, 2940, 2840, 1600, 1500, 1270, 1140, 1105, 980 cm^{-1}; NMR (CCl_4) δ 3.4 (s, 3 H), 3.6 (s, 6 H), 6.6 (d, 2 H, J = 8.0 Hz), 7.2 (m, 11 H), 7.9 (d, 1 H, J = 6.0 Hz), 11.0 (broad s, 1 H). The broad singlet at δ 11.0 disappeared on addition of a drop of deuterated water to the NMR sample.

Anal. Calcd for $C_{28}H_{24}N_2O_3$: C, 77.05; H, 5.54; N, 6.42. Found: C, 76.36; H, 5.50; N, 6.45.

Reaction of 2-*p*-Anisoyl-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with Styrene. The procedure utilized for the reaction between the Reissert salt **4** (R = C_6H_5) and styrene was used. In this particular cycloaddition, 5 equiv of styrene and a reaction time of 24 h were employed. The yield of the product (**10**) was 60%: mp 198–200 °C; IR (KBr) 2940, 2840, 1470, 1420, 1250, 1125, 835, 770 cm^{-1}; NMR (CCl_4) δ 3.3 (s, 3 H), 3.5 (s, 3 H), 3.8 (s, 3 H), 3.9 (s, 3 H), 6.5 (d, 2 H, J = 9.0 Hz), 12.8 (broad s, 1 H). The broad singlet at δ 12.8 disappeared on addition of a drop of deuterated water to the NMR sample.

Anal. Calcd for $C_{29}H_{26}N_2O_4$: N, 6.00. Found: N, 5.93.

Reaction of 2-*p*-Anisoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with 1-(3,4-Dimethoxyphenyl)propene. The procedure utilized for the reaction between this particular Reissert salt and styrene was used. The yield of product (**7**) was 30%: mp 159–160 °C; IR ($CHCl_3$) 3450, 2940, 2840, 1580, 1140, 1120, 1020, 980, 865, 840 cm^{-1}; NMR (CCl_4) δ 2.3 (s, 3 H), 3.35 (s, 3 H), 3.45 (s, 3 H), 3.7 (s, 9 H), 6.5 (m, 5 H), 7.2 (m, 5 H), 8.0 (d, 1 H, J = 5.0 Hz), 11.2 (broad s, 1 H). The broad singlet at δ 11.2 disappeared on addition of a drop of deuterated water to the NMR sample.

Anal. Calcd for $C_{31}H_{30}N_2O_5$: C, 72.93; H, 5.92; N, 5.48. Found: C, 73.13; H, 5.90; N, 5.34.

Reaction of 2-*p*-Anisoyl-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with 1-(3,4-Dimethoxyphenyl)propene. The procedure utilized for the reaction between this specific Reissert salt and styrene was used. In this particular condensation, a reaction temperature of 150 °C was employed. The yield of product (**11**) was 13%: mp 134–136 °C; IR (KBr) 2940, 2840, 1510, 1470, 1250, 1120, 1025, 845 cm^{-1}; NMR ($CDCl_3$) δ 2.4 (s, 3 H), 3.3 (s, 3 H), 3.5 (s, 3 H), 3.6 (s, 3 H), 3.8 (s, 3 H), 3.9 (s, 6 H), 6.5–7.3 (m, 8 H), 7.5 (d, 1 H, J = 6.0 Hz), 7.9 (d, 1 H, J = 6.0 Hz), 12.4 (broad s, 1 H). The broad singlet at δ 12.4 disappeared on the addition of a drop of deuterated water to the NMR sample.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate 4 (R = C_6H_5) with *trans*-Stilbene. The procedure utilized for the reaction between **4** (R = C_6H_5) and styrene was used. When 1 equiv of *trans*-stilbene and a reaction time of 24 h were employed, the yield of **16** was 34%. Use of 30 equiv of *trans*-stilbene under the above conditions increased the yield to 60%, mp 268–270 °C (lit.[19] mp 262.5–263.5 °C).

This compound showed no depression in a mixture melting point test with authentic 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**16**), and the infrared spectra of the two samples, taken in chloroform solution, were identical.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C_6H_5) with *N*-Phenylmaleimide. The procedure utilized for the reaction between **4** (R = C_6H_5) and styrene was used. In this particular condensation, 5 equiv of *N*-phenylmaleimide, a reaction temperature of 150 °C, and a reaction time of 50 h were employed. The yield of **9** was 42%: mp 293–294 °C dec; IR ($CHCl_3$) 3420, 1750, 1700, 1490, 1350, 1090, 875 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (s, 5 H), 7.4 (m, 7 H), 7.7 (m, 3 H), 8.5 (d, 1 H, J = 6.0 Hz).

Anal. Calcd for $C_{27}H_{17}N_3O_2$: C, 78.06; H, 4.12; N, 10.11. Found: C, 77.52; H, 4.11; N, 9.89.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C_6H_5) with Diethyl Maleate. The procedure utilized for the reaction between **4** (R = C_6H_5) and *N*-phenylmaleimide was used. The yield of **8** was 54%: mp 179–180°C; IR ($CHCl_3$) 2980, 1720, 1670, 1310, 1265, 1100, 1035, 980 cm^{-1}; NMR ($CDCl_3$) δ 0.68 (t, 3 H, J = 6.4 Hz), 1.60 (t, 3 H, J = 6.4 Hz), 3.90 (q, 2 H, J = 6.4 Hz), 4.30 (q, 2 H, J = 6.4 Hz), 7.30 (m, 6 H), 7.66 (m, 4 H), 8.25 (m, 1 H), 13.45 (broad s, 1 H). The broad singlet at δ 13.45 disappeared on the addition of a drop of deuterated water to the NMR sample.

Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.51; H, 5.27; N, 6.68.

Reaction of 2-Acetyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = CH_3) with Dimethyl Maleate. A slurry of 2.86 g (0.010 mol) of **4** (R = CH_3), 30 mL of methylene chloride, and 3.0 mL of dimethyl maleate was heated to boiling with stirring and then refluxed for 20 min. Next, 75 mL of 95% ethanol was added in small portions during 10 min. Reflux was continued for an hour. Finally, stirring at room temperature was continued for an additional 1.25 h. The reaction solution was concentrated, yielding a viscous light orange oil. The oil was dissolved in benzene–chloroform and chromatographed on neutral alumina (activity I), packed in benzene–chloroform (2:1). The relative amount of chloroform was gradually increased, and when solid began to be eluted from the column pure chloroform was used as the solvent. The product, dimethyl 2-(1-isoquinolyl)-5-methylpyrrole-3,4-dicarboxylate (**12**) (which was recrystallized from benzene), was obtained by evaporation of the eluent of the broad yellow band. There was obtained 2.45 g (76%) of the compound: mp 138.5–140.0 °C; IR ($CHCl_3$) 3440, 3000, 2960, 1710, 1640, 1590, 1560, 1510, 1450, 1385, 1300, 1205, 1100, 945, 830 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.35 (s, 3 H), 3.85 (s, 3 H), 7.70 (m, 6 H).

Reaction of 2-Isobutyryl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = Isopropyl) with Dimethyl Maleate. The procedure utilized for the reaction between the Reissert salt **4** (R = CH_3) and dimethyl maleate was used. The yield of dimethyl 2-(1-isoquinolyl)-5-isopropylpyrrole-3,4-dicarboxylate (**13**) was 68%: mp 165–166 °C (recrystallized from methanol–water); IR ($CHCl_3$) 3440, 2950, 1710, 1620, 1590, 1450, 1385, 1335, 1280, 1215, 1090, 815 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, 6 H, J = 7.2 Hz), 3.35 (s, 3 H), 3.60 (m, 1 H), 3.85 (s, 3 H), 7.60 (m, 6 H).

Anal. Calcd for $C_{26}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95; O, 18.16. Found: C, 68.28; H, 5.75; N, 7.90; O, 18.14.

Reaction of 2-(Cyclopropanecarbonyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = Cyclopropyl) with Dimethyl Maleate. The procedure utilized for the reaction between the Reissert salt **4** (R = CH_3) and dimethyl maleate was used. However, concentrating the reaction solution yielded almost exclusively the hydrofluoroborate salt of dimethyl 2-(1-isoquinolyl)-5-cyclopropylpyrrole-3,4-dicarboxylate (**14**). This crude salt was digested for 10 min in 75 mL of benzene and collected by filtration. The solid, which was recrystallized from methanol, accounted for 65% yield of hydrofluoroborate salt, mp 238 °C dec. The filtrate was concentrated and dissolved in chloroform, a small amount of dry column alumina was added, and the mixture was then evaporated to dryness. According to the method preferred by Loev and Goodman,[20] the residual solid was placed on a silica gel dry column. The column was developed with methylene chloride. Only the band furthest down (relatively broad, colorless) of the three bands visible under UV light yielded the desired product, dimethyl 2-(1-isoquinolyl)-5-cyclopropylpyrrole-3,4-dicarboxylate (**14**) (5.3%). The compound was recrystallized from methanol–water, mp 186.0–188.5 °C. The remaining two bands proved to contain mixtures of several components and were therefore not examined further.

The hydrofluoroborate salt described above was suspended in 20 mL of water. Sodium hydroxide solution (10%) was added until the mixture remained weakly alkaline to pH paper. The white solid which formed was collected by filtration and washed with water. The conversion, which was quantitative, gave, after recrystallization from methanol–water, a compound of mp 187.5–189 °C. A mixture melting point test of this compound with the compound isolated by column chromatography showed no depression: IR ($CHCl_3$) 3430, 3000, 1705, 1620, 1595, 1560, 1520, 1500, 1465, 1390, 1320, 1280, 1095, 1070, 1015, 995, 945, 895, 810 cm^{-1}; NMR ($CDCl_3$) δ 0.65 (m, 4 H), 2.50 (m, 1 H), 3.35 (s, 3 H), 3.85 (s, 3 H), 7.70 (m, 6 H).

Reaction of 2-(1-Naphthoyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = Naphthyl) with Dimethyl Maleate. The procedure utilized for the reaction between the Reissert salt **4** (R = CH_3) and dimethyl maleate was used. In this particular condensation, after the addition of 95% ethanol, dimethylformamide was added until the salt went into solution. As in the condensation of the Reissert salt **4** (R = cyclopropyl) with dimethyl maleate, dry column chromatography was employed to separate the components of the reaction mixture. The desired product, dimethyl 2-(1-isoquinolyl)-5-(1-naphthyl)pyrrole-3,4-dicarboxylate (**15**), crystallized from methanol–water, was isolated in 37% yield: mp 117–122 °C; IR ($CHCl_3$) 3420, 3070, 2950, 1710, 1625, 1585, 1550, 1500, 1450, 1390, 1260, 1200, 1145, 1095, 1055, 965, 935, 860, 815, 720 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (s, 3 H), 3.50 (s, 3 H), 7.50 (m, 13 H).

C. Reactions of Reissert Hydrofluoroborate Salts with Alkynes. Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C_6H_5) with Phenylacetylene. A mixture of 2.3 g (6.6 mmol) of Reissert salt **4** (R = C_6H_5), 1.33 g (13.0 mmol) of phenylacetylene, and 20 mL of anhydrous *N,N*-dimethylformamide was stirred for 24 h at 120 °C. The reaction mixture was poured into 500 mL of water, and the aqueous suspension was ex-

tracted with ten 100-mL portions of benzene. The benzene extract was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated almost to dryness. The concentrated solution was chromatographed on neutral alumina (activity I[18]), with a benzene–chloroform mixture (1:1) being used as the eluent. The first fraction which was eluted from the column gave 1.2 g (57%) of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline (**17**), mp 138–140 °C (lit. mp 136–138 °C). The remaining fraction gave 0.18 g (7.5%) of 2-(1-isoquinolyl)-3,5-diphenylpyrrole (**5**), mp 229–231 °C. A mixture melting point test of this compound and the product of the reaction of the Reissert salt with styrene showed no depression.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C_6H_5) with Diphenylacetylene (Tolan). A mixture of 6.8 g (0.0195 mol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate and 10.7 g (0.6 mol) of tolan was refluxed for 24 h in 60 mL of anhydrous DMF which had been dried and stored over molecular sieves. The mixture was cooled, poured into 200 mL of water, and neutralized with solid sodium bicarbonate. The mixture was extracted with three 60-mL portions of benzene, and the benzene extracts were combined, washed several times with water, and dried over anhydrous sodium sulfate. The benzene was evaporated, leaving an oily black residue.

This residue was chromatographed on a CAMAG neutral alumina column prepared in benzene. Elution with benzene yielded a pale yellow fraction which was strongly blue fluorescent. A second fraction was eluted with a 1:1 mixture (v/v) of chloroform and ethyl acetate. It was composed of three overlapping bands on the column: a narrow orange band, a broad yellow band, and a narrow brown band. The solvent was evaporated from the first fraction, and a yellow gum was obtained as the residue. This was dissolved in a small amount of chloroform, and some Woelm dry column silica gel was added. The solvent was evaporated in vacuo, and the residual solid was placed on a silica gel dry column. This is the method preferred by Loev and Goodman.[20] The column was eluted with petroleum ether until evaporation of an aliquot of the eluent left no solid residue. There was obtained 8.75 g (82%) of pure tolan. The yellow (blue fluorescent) band remaining near the top of the column was removed mechanically, and the adsorbed material was extracted into a mixture of chloroform and ethanol. The solvent was evaporated to give 2.15 g (28%) of a pale yellow compound, which subsequently proved to be nearly pure 1,2,3-triphenylpyrrolo[2,1-*a*]isoquinoline (**18**), mp 165–169 °C. This material was dissolved in 25 mL of chloroform. To this solution was added 25 mL of 95% ethanol. The solution was concentrated to 12 mL, and the solution was cooled to yield small, slightly off-white, crystals: mp 178–179 °C; IR ($CHCl_3$) 3060, 1960, 1890, 1810, 1605, 1480, 1385, 1370, 1295, 1120, 1080, 1020, 910, 870 cm^{-1}; NMR ($CDCl_3$) δ 6.6 (d, 1 H, J = 8.0 Hz), 7.25 (m, 19 H), 7.75 (d, 1 H, J = 9.0 Hz).

Anal. Calcd for $C_{30}H_{21}N$: C, 91.09; H, 5.32; N, 3.59. Found: C, 90.99; H, 5.39; N, 3.51.

The solvent was evaporated from the second fraction obtained from the initial neutral alumina column, and the residue was chromatographed on a Woelm silica gel dry column with benzene as the eluent. The first band was narrow and red; the second band was broad and yellow (blue fluorescent). The second band was removed mechanically, and the adsorbed material was extracted into a mixture of chloroform and ethanol. Evaporation of the solvent gave 0.635 g of a yellow powder. This material was decolorized by use of activated carbon and crystallized from a 2:1 mixture (v/v) of ethanol and chloroform. There was obtained 0.505 g (6.42%) of 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**16**), mp 269–270 °C. A mixture melting point test with an authentic sample showed no depression. Also, the IR and NMR spectra were identical with the corresponding spectra of an authentic sample.[9]

2-(α-Bromobenzyl)-2-phenyl-1,3-dioxolane. A solution of 10.0 g of desyl bromide, 4.0 g of ethylene glycol, and a small amount of *p*-toluenesulfonic acid in toluene was refluxed in a Dean-Stark apparatus until no more water could be removed. The solution was washed with two 50-mL portions of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting residue was recrystallized from absolute ethanol. There was obtained 9.62 g (82%) of 2-(α-bromobenzyl)-2-phenyl-1,3-dioxolane as colorless prisms, mp 104–106 °C.

1,2,3-Triphenylpyrrolo[2,1-*a*]isoquinoline (18). A solution of 1.0 g of 1-benzylisoquinoline in 25 mL of a 1:1 mixture (v/v) of anhydrous benzene and anhydrous ether was stirred under nitrogen as 2 mL of 2.3 N phenyllithium solution (Alfa-Inorganics Inc.) was added dropwise. The solution immediately became dark red in color. A solution of 1.5 g of 2-(α-bromobenzyl)-2-phenyl-1,3-dioxolane in 25 mL of anhydrous ether was added slowly, and the solution was stirred for 4 h, at the end of which time the color had become yellow-brown. The solution was added to 100 mL of water and extracted with two 50-mL portions of chloroform. The organic extracts were combined, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a gummy yellow residue. The residue was stirred at 130 °C with 20 mL of polyphosphoric acid for 30 min. The mixture was cooled, diluted with water, and neutralized by the addition of 10% sodium hydroxide solution. The mixture was extracted with two 50-mL portions of chloroform. The organic extracts were combined, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a gummy brown residue which was placed on a silica gel dry column[20] and eluted with benzene. The material obtained from the first blue fluorescent band was chromatographed on a second silica gel dry column, with petroleum ether being used as the eluent. The blue fluorescent band remaining at the top of the second column was removed mechanically, and the adsorbed material was removed by extraction into a mixture of chloroform and ethanol. Evaporation of the solvent gave 0.04 g (2.25%) of crude 1,2,3-triphenylpyrrolo[2,1-*a*]isoquinoline (**18**) as a brown powder. This material was twice recrystallized from a 1:1 mixture (v/v) of chloroform and ethanol. There was obtained a small quantity of pale yellow powder, mp 177–178 °C. Its IR spectrum, taken in chloroform solution, and its NMR spectrum, taken in chloroform-d_1 solution, were identical with those of the supposed 1,2,3-triphenylpyrrolo[2,1-*a*]-isoquinoline (**18**), mp 178–179 °C, obtained from the reaction of the Reissert salt with tolan. A mixture melting point test of the two samples showed no depression.

Reaction of 2-Acetyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = CH_3) with Dimethyl Acetylenedicarboxylate. A mixture of 3.40 g (1.19×10^{-2} mol) of the Reissert salt **4** (R = CH_3), 6.0 mL of dimethyl acetylenedicarboxylate, and 75 mL of anhydrous DMF was stirred at 100 °C for 22 h. The reaction mixture was poured into 300 mL of water, and the aqueous suspension was extracted with ten 100-mL portions of benzene. The benzene extract was dried over powdered Drierite and filtered, and the filtrate was concentrated almost to dryness. The concentrated solution was chromatographed on neutral alumina (activity I[18]), with a benzene–chloroform mixture (1:4) being used as the eluent. The eluent from the first band (broad, pale yellow) yielded 2.25 g (64%) of dimethyl 3-methylpyrrole[2,1-*a*]isoquinoline-1,2-dicarboxylate (**19**), mp 175.5–176.0 °C (recrystallized from methanol–water). Subsequent fractions yielded only material which was polymeric in nature: IR ($CHCl_3$) 3010, 2960, 1720, 1530, 1445, 1405, 1365, 1300, 1285, 1220, 1155, 1100, 1070, 1015, 950, 915 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (s, 3 H), 3.05 (s, 3 H), 3.15 (s, 3 H), 5.90 (d, 1 H J = 9.0 Hz), 6.60 (m, 4 H), 7.40 (m, 1 H).

Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.08; N, 4.71; O, 21.53. Found: C, 68.41; H, 5.21; N, 4.80; O, 21.67.

Reaction of 2-Isobutyryl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = Isopropyl) with Dimethyl Acetylenedicarboxylate. The procedure utilized for the reaction between the Reissert salt **4** (R = CH_3) and dimethyl acetylenedicarboxylate was used. In this particular condensation, 100% chloroform was employed as the eluent for column chromatography. The eluent from the first fraction gave a 26% yield of dimethyl 3-isopropylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**20**): mp 111.0–112.0 °C (recrystallized from methanol–water); IR ($CHCl_3$) 2960, 1710, 1515, 1465, 1440, 1360, 1335, 1270, 1200, 1105, 1075, 1050, 1000, 950, 720 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (d, 6 H, J = 8.0 Hz), 3.70 (m, 1 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 6.75 (d, 1 H, J = 9.0 Hz), 7.40 (m, 3 H), 7.70 (d, 1 H, J = 9.0 Hz), 8.70 (m, 1 H).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.24; H, 5.94; N, 4.43.

Reaction of 2-(Cyclopropanecarbonyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = Cyclopropyl) with Dimethyl Acetylenedicarboxylate. The procedure utilized for the reaction between the Reissert salt **4** (R = CH_3) and dimethyl acetylenedicarboxylate was used. In this particular condensation, benzene–chloroform (2:1) was employed as the eluent for column chromatography. The eluent from the first fraction gave a 47% yield of dimethyl 3-cyclopropylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**21**): mp 131.0–131.5 °C (recrystallized from methanol–water); IR ($CHCl_3$) 3000, 2950, 1710, 1505, 1440, 1405, 1360, 1315, 1300, 1275, 1205, 1150, 1105, 1050, 1000, 950, 915, 820 cm^{-1}; NMR ($CDCl_3$) δ 0.65 (m, 2 H), 1.05 (m, 2 H), 1.75 (m, 1 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 6.75 (d, 1 H, J = 9.0 Hz), 7.35 (m, 3 H), 7.90 (d, 1 H, J = 9.0 Hz), 8.75 (m, 1 H).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.42; H, 5.19; N, 4.34.

Reaction of 2-(1-Naphthoyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = 1-Naphthyl) with Dimethyl

Acetylenedicarboxylate. A mixture of 1.58 g (3.96×10^{-3} mol) of the Reissert salt **4** (R = 1-naphthyl), 2.0 mL of dimethyl acetylenedicarboxylate, and 25 mL of anhydrous DMF was stirred at 100 °C for 22 h. The reaction mixture was concentrated and then poured into 130 mL of water. A light yellow-brown solid which formed was collected by suction filtration. This crude material (3.05 g) was chromatographed on a dry column,[20] with methylene chloride being used as eluent. A pale yellow solid (0.62 g, 38%) was eluted. Recrystallization of the solid, identified as dimethyl 3-(1-naphthyl)pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**22**), from methanol gave a pure product: mp 195.5–196.5 °C; IR ($CHCl_3$) 3030, 2960, 1715, 1600, 1515, 1450, 1405, 1360, 1300, 1215, 1095, 1055, 1005, 970, 940, 910, 760 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (s, 3 H), 4.00 (s, 3 H), 6.55 (d, 1 H, J = 9.0 Hz), 6.95 (d, 1 H, J = 9.0 Hz), 7.40 (m, 8 H), 7.85 (m, 2 H), 8.55 (m, 1 H).

Anal. Calcd for $C_{26}H_{19}NO_4$: C, 76.27; H, 4.68; N, 3.42. Found: C, 75.96; H, 4.80; N, 3.26.

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Registry No.—**5,** 53778-23-7; **6,** 68001-15-0; **7,** 68001-16-1; **8,** 68001-17-2; **9,** 68001-18-3; **10,** 68001-19-4; **11,** 68001-20-7; **12,** 68001-21-8; **13,** 68001-22-9; **14,** 68001-23-0; **15,** 68001-24-1; **16,** 10425-52-2; **17,** 20958-81-0; **18,** 51039-56-6; **19,** 34977-08-7; **20,** 68001-39-8; **21,** 68001-40-1; **22,** 68001-41-2; 2-*p*-anisoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile, 68001-42-3; 2-*p*-anisoyl-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile, 68001-43-4; 2-acetyl-1,2-dihydroisoquinaldonitrile, 29924-67-2; 2-isobutyryl-1,2-dihydroisoquinaldonitrile, 68001-44-5; 2-(cyclopropanecarbonyl)-1,2-dihydroisoquinaldonitrile, 68001-45-6; 2-(1-naphthoyl)-1,2-dihydroisoquinaldonitrile, 21259-46-1; 2-(α-bromobenzyl)-2-phenyl-1,3-dioxolane, 68001-46-7; potassium cyanide, 151-50-8; isoquinoline, 119-65-3; 1-naphthoyl chloride, 879-18-5; desyl bromide, 1484-50-0; ethylene glycol, 107-21-1; 1-benzylisoquinoline, 6907-59-1; phenyllithium, 591-51-5.

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Hindered Rotation in Hexasubstituted Guanidine Salts

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Proton NMR spectra of 2,2-dibenzyl-1,1,3,3-tetramethylguanidine chloride and 2,2-dixylyl-1,1,3,3-tetramethylguanidine chlorides were examined. All compounds exhibited temperature dependent resonances for both the $-N(CH_3)_2$ and $-N(CH_2Ar)_2$ protons. This temperature dependence is consistent with the view that restricted rotation exists for the three major C=N bonds of the guanidine nucleus. The results provide evidence for the existence of a nonplanar structure for hexasubstituted guanidine salts.

Syn–anti isomerization of double-bonded nitrogen in free guanidines has been observed[1-4] by their temperature dependent NMR spectra. Kessler and co-workers[1,2] have shown convincingly that this syn–anti conversion is a true inversion process involving an sp hybridized nitrogen atom in the transition state. A similar NMR temperature dependence has been observed for the salts of 2-aryl-1,1,3,3-tetramethylguanidine.[1] Two mechanisms which have been proposed are rotation about the C=N bond or deprotonation to the free guanidine followed by inversion and protonation. The authors considered rotation about the C=N bond to be more likely for three reasons. First, in tetramethyl-2-alkylguanidine salts[5] vicinal coupling of the NH protons with the α protons of the alkyl group occurs at room temperature while simultaneously the signal of the dimethylamino protons appears as a sharp singlet. Secondly, the free energy of activation of proton exchange was shown to be larger than the free energy of activation for the syn–anti conversion. Finally, they reported finding similar free energy of activation barriers for pentamethylarylguanidine iodine salts.[6]

In our study of 2,2-dibenzyl- and 2,2-dixylyl-1,1,3,3-tetramethylguanidine salts similar rotation barriers were found. In this report we present the results of NMR studies and their implications concerning a new aspect of the structure of highly substituted guanidine salts.

Results and Discussion

The synthesis of the hexasubstituted guanidine halides is outlined in Scheme I. The reaction carried out in benzene is quite exothermic and goes essentially to completion without heating of the reaction mixture. Under these conditions the guanidine salts precipitate from the reaction mixture as fine needles. If the reaction is carried out with equal molar quantities of tetramethylguanidine (TMG, **1**) and benzyl halide,

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