Synthetic Uses of Open-Chain Analogues of Reissert Compounds

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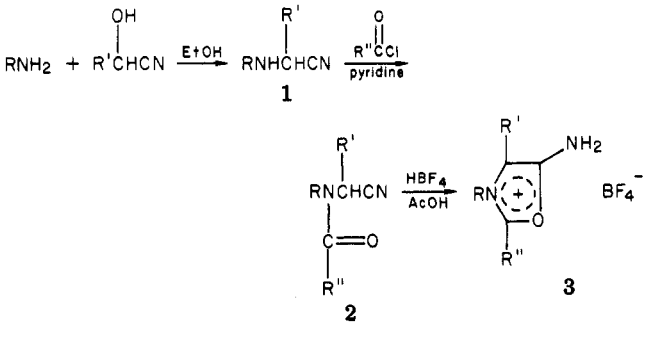
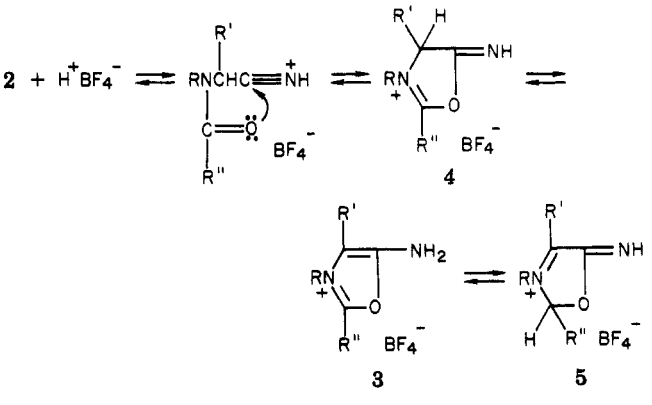
Open-chain analogues, **2**, of Reissert compounds are readily obtained by reaction of cyanohydrins with primary amines, the resulting aminonitriles, **1**, then being acylated. Hydrofluoroborate salts, **3**, of **2** are prepared by reaction with fluoroboric acid in glacial acetic acid. The salts, **3**, undergo 1,3-dipolar addition reactions with reactive alkynes to give substituted pyrroles and with ethyl acrylate to give a different type of substituted pyrrole, the initial step in this instance being a Diels–Alder reaction. The open-chain Reissert analogues **2** also undergo base-catalyzed reactions, such as alkylation to provide compounds **22**, which, in turn, undergo cleavage reactions in ethanolic alkali to give ketones **23**. A conjugate addition reaction of the anion **18** to methyl acrylate to give, after some subsequent steps, a substituted pyrrole, **9**, has also been demonstrated. α-Anilino ketones **27** result when the anion **18** is caused to react with aldehydes, the initial reaction mixtures being subjected to subsequent alkaline hydrolysis. Finally, *N*-benzyl Reissert analogues have been found to give desoxybenzoins plus benzonitriles on treatment with sodium hydride in tetrahydrofuran.

Reissert compounds are versatile intermediates in the synthesis of diverse heterocyclic compounds.[1-3] Most of the applications have been with isoquinoline Reissert compounds, but other heterocyclic nitrogen compounds have also been subjected to analogous sequences of reactions. As applied to isoquinoline Reissert compounds, base-catalyzed alkylation with alkyl halides, with subsequent alkaline cleavage of the alkylated products, produces 1-alkylisoquinolines.[4-8] Base-catalyzed condensation–rearrangement reactions with aldehydes give esters of 1-isoquinolylalkyl (or -aryl) carbinols.[7,9] Base-catalyzed conjugate addition reactions[5] and rearrangements[10] have been reported. Many acid-catalyzed reactions of Reissert compounds have also been described. Perhaps the best known of these is the preparative method for aldehydes known as the Reissert reaction.[12-15] Recently, acid-catalyzed reactions of Reissert compounds with alkenes[16-20] and alkynes[16,18,21-23] have been reported in the literature.

Scheme I



Scheme II



Several open-chain analogues of Reissert compounds have been prepared and subjected to acid-catalyzed hydrolysis.[5,24,25] However, since carboxylic acids rather than aldehydes were obtained, these compounds were considered not to be completely analogous to Reissert compounds prepared from isoquinoline, quinoline, and other heterocyclic bases. Open-chain analogues of Reissert salts have also been prepared, but no significant chemistry of such compounds has been described.[26-28] Since open-chain analogues of Reissert compounds and their salts had the

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Table I. Reactions of RNH_2 with R'CH(OH)CN to Produce RNHCR'HCN (1) and Physical Properties of the Products

R	R'	product	yield, %	mp, °C	NMR data ($CDCl_3$), δ (J in Hz)
C_6H_5	C_6H_5	1a	66	81-83[a]	7.05 (m, 10 H), 5.31 (d, 1 H, J = 9), 4.14 (d, 1 H, J = 9)
m-ClC_6H_4	C_6H_5	1b	70	77-79[b]	7.00 (m, 9 H), 5.34 (d, 1 H, J = 9), 4.20 (d, 1 H, J = 9)
p-$MeOC_6H_4$	C_6H_5	1c	77	74-76[c]	7.40 (m, 9 H), 6.30 (d, 1 H, J = 11), 5.80 (d, 1 H, J = 11), 3.1 (s, 3 H)
$C_6H_5CH_2$	C_6H_5	1d	74	30-32[d]	7.02 (m, 10 H), 4.55 (d, 1 H, J = 10), 3.8 (d, 2 H, J = 5), 2.8 (m, 1 H)
$C_6H_5CH_2$	H	1e		oil[e]	
C_6H_5	p-ClC_6H_4	1f	75	110-111[f]	7.10 (m, 9 H), 5.35 (d, 1 H, J = 8), 4.05 (d, 1 H, J = 8)
C_6H_5	m-ClC_6H_4	1g	45	80-81[g]	7.10 (m, 9 H), 5.36 (d, 1 H, J = 8), 4.15 (d, 1 H, J = 8)
C_6H_5	o-ClC_6H_4	1h	46	75-76[h]	7.17 (m, 9 H), 5.68 (d, 1 H, J = 8), 4.20 (d, 1 H, J = 8)
C_6H_5	3,4-$(Me)_2OC_6H_3$	1i	32	146-147[i]	7.05 (m, 8 H), 5.32 (d, 1 H, J = 7), 4.16 (d, 1 H, J = 7), 3.83 (s, 3 H), 3.82 (s, 3 H)
C_6H_5	m-$MeOC_6H_4$	1j	25	59-60[j]	7.03 (m, 9 H), 5.38 (d, 1 H, J = 5), 4.12 (d, 1 H, J = 5), 3.78 (s, 3 H)
C_6H_5	o-$MeOC_6H_4$	1k	74	60-61[k]	7.05 (m, 9 H), 5.52 (d, 1 H, J = 9), 4.40 (d, 1 H, J = 9), 3.70 (s, 3 H)
C_6H_5	n-C_4H_9	1l	99	57-58[l]	6.96 (m, 5 H), 4.00 (m, 2 H), 1.39 (m, 9 H)
p-$ClC_6H_4CH_2$	C_6H_5	1m	80	41-43[m]	7.04 (m, 9 H), 4.70 (s, 1 H), 3.90 (s, 2 H), 1.80 (s, 1 H)
n-C_5H_{11}	C_6H_5	1n		oil[n]	
c-C_6H_{11}	C_6H_5	1o	88	56-57[o]	7.04 (m, 5 H), 4.80 (s, 1 H), 2.80 (br s, 1 H), 1.50 (m, 12 H)
m-$MeOC_6H_4$	C_6H_5	1p	55	57-59[p]	
p-ClC_6H_4	C_6H_5	1q	70	78-80[q]	6.95 (m, 9 H), 5.25 (d, 1 H, J = 8), 4.22 (d, 1 H, J = 8)
2,4,6-$(Me)_3C_6H_2$	C_6H_5	1r	64	80-82[r]	7.25 (m, 7 H), 5.25 (d, 1 H, J = 11), 4.80 (d, 1 H, J = 11), 2.20 (d, 9 H, J = 6)

[a] Reported,[25] mp 85 °C. [b] Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54. Found: C, 69.04; H, 4.55; N, 11.46. [c] Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.63; H, 5.85; N, 11.82. [d] Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.61. Found: C, 80.87; H, 6.56; N, 12.55. [e] Converted into the N-benzoyl derivative 2e without purification and characterization. [f] Reported,[50] mp 112-113 °C. [g] Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.24; H, 4.67; N, 11.44; Cl, 14.55. [h] Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.15; H, 4.65; N, 11.48; Cl, 14.88. [i] Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 72.62; H, 6.01; N, 10.44. Found: C, 71.53; H, 6.26; N, 10.49. [j] Anal. Calcd for $C_{15}H_{11}N_2O$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.59; H, 6.19; N, 11.64. [k] Anal. Calcd for $C_{15}H_{11}N_2O$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.43; H, 6.12; N, 11.82. [l] Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.49; H, 8.61; N, 14.87. [m] Anal. Calcd for $C_{15}H_{13}N_2Cl$: C, 70.17; H, 5.10; N, 10.91; Cl, 13.81. Found: C, 70.19; H, 5.05; N, 10.92; Cl, 13.90. [n] Converted into N-benzoyl derivative without purification and characterization. [o] Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.46; N, 13.08. Found: C, 78.71; H, 8.71; N, 13.30. [p] Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.47; H, 5.87; N, 11.63. [q] Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.23; H, 4.66; N, 11.54; Cl, 14.52. [r] Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.50; H, 7.35; N, 11.13.

potential to be useful intermediates in the synthesis of pyrroles and nonheterocyclic compounds, we undertook an intensive investigation of such possible applications.

Preparation of Open-Chain Analogues of Reissert Compounds. The general procedure that was used for the preparation of open-chain analogues of Reissert compounds involved first the preparation of an aminonitrile by condensation of a primary amine with a cyanohydrin. The aminonitrile was then caused to react with an acid chloride to form the Reissert compound (Scheme I). The properties of these compounds are given in Tables I and II.

Acid-Catalyzed Reactions of Reissert Compounds. Each Reissert salt analogue, 3, was prepared by dissolving the corresponding Reissert analogue, 2, in a minimum amount of glacial acetic acid and adding a 48% solution of fluoroboric acid. Upon addition of ether, each Reissert analogue salt precipitated in the form of fine pale yellow crystals which were analytically pure if pure Reissert compound analogue was used in the reaction. The properties of these salts are given in Table III.

The mechanism for the formation of the salts is thought to be analogous to that of the formation of the quinoline and isoquinoline Reissert salts. The nitrile nitrogen is protonated by the acid, and intramolecular nucleophilic attack by the carbonyl oxygen on the nitrile carbon results in ring closure to give an oxazolium ring system (Scheme II), which can exist as an equilibrium mixture of tautomeric forms, of which 3 is undoubtedly the predominant one.[29,30]

The salts of the Reissert analogues can also dissociate to give mesoionic compounds which are analogous to munchnones[31-36] (actually munchnone imines). It was

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Table II. Yields and Physical Properties of 2

	R	R′	R″	yield, %	mp, °C	NMR data ($CDCl_3$), δ (J in Hz)
2a	C_6H_5	C_6H_5	C_6H_5	81	86.5-88.5[a]	7.25 (m)
b	m-ClC_6H_4	C_6H_5	C_6H_5	69	114.5-116[b]	7.00 (m)
c	p-$MeOC_6H_4$	C_6H_5	C_6H_5	72	63-65[c]	7.25 (m, 15 H), 3.55 (s, 3 H)
d	$C_6H_5CH_2$	C_6H_5	C_6H_5	87	137-138[d]	7.30 (m, 15 H), 6.60 (s, 1 H), 4.50 (d, 2 H, J = 15)[e]
e	$C_6H_5CH_2$	H	C_6H_5	43	176-178	7.40 (m, 10 H), 4.67 (s, 2 H), 4.22 (s, 2 H)
f	C_6H_5	p-ClC_6H_4	C_6H_5	87	95-96[f]	7.08 (m)
g	C_6H_5	m-ClC_6H_4	C_6H_5	72	112-113.5[g]	7.25 (m)
h	C_6H_5	o-ClC_6H_4	C_6H_5	82	138-139[h]	7.08 (m)
i	C_6H_5	3,4-$(MeO)_2OC_6H_3$	C_6H_5	89	135-136[i]	7.13 (m, 14 H), 3.82 (s, 3 H), 3.73 (s, 3 H)
j	C_6H_5	m-$MeOC_6H_4$	C_6H_5	88	85-86[j]	7.13 (m, 15 H), 3.68 (s, 3 H)
k	C_6H_5	o-$MeOC_6H_4$	C_6H_5	94	141-142[k]	7.05 (m, 15 H), 3.84 (s, 3 H)
l	C_6H_5	n-C_4H_9	C_6H_5	89	64-65[l]	7.21 (m, 10 H), 5.81 (t, 1 H, J = 7.5), 1.37 (m, 9 H)
m	p-$ClC_6H_4CH_2$	C_6H_5	C_6H_5	85	140-142[m]	
n	n-C_6H_{13}	C_6H_5	C_6H_5	61	65-66[n]	7.50 (m, 10 H), 6.60 (s, 1 H), 1.10 (m, 13 H)
o	c-C_6H_{11}	C_6H_5	C_6H_5	57	178-180[o]	
p	m-$MeOC_6H_4$	C_6H_5	C_6H_5	54	115-117[p]	7.02 (m, 15 H), 5.55 (s, 3 H)
q	p-ClC_6H_4	C_6H_5	C_6H_5	44	103-104[q]	7.10 (m, 14 H), 6.70 (s, 1 H)
r	2,4,6-$(Me)_3C_6H_2$	C_6H_5	CH_3	50	138-140[r]	
s	C_6H_5	H	C_6H_5	64	99-100[s]	
t	p-$MeOC_6H_4CH_2$	C_6H_5	C_6H_5	64	121-123[t]	7.2 (m, 14 H), 6.45 (s, 1 H), 4.55 (d, 2 H, J = 6),[e] 3.75 (s, 3 H)
u	$C_6H_5CH_2$	p-$MeOC_6H_4$	C_6H_5	50	125-127[u]	7.25 (m, 14 H), 6.45 (s, 2 H), 3.8 (s, 3 H)

[a] Reported,[25] mp 87-88 °C. [b] Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.72; H, 4.36; N, 8.08. Found: C, 72.82; H, 4.61; N, 8.06. [c] Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.05; H, 5.22; N, 7.95. [d] Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.56; N, 8.59. Found: C, 80.84; H, 5.59; N, 8.61. [e] Diastereotopic splitting of the CH_2 group. [f] Anal. Calcd for $C_{21}H_{15}N_2OCl$: C, 72.73; H, 4.36; N, 8.08; Cl, 10.22. Found: C, 72.79; H, 4.51; N, 8.10; Cl, 10.23. [g] Anal. Calcd for $C_{21}H_{15}N_2OCl$: C, 72.73; H, 4.36; N, 8.09; Cl, 10.22. Found: C, 72.59; H, 4.34; N, 8.05; Cl, 10.33. [h] Anal. Calcd for $C_{21}H_{15}N_2OCl$: C, 72.73; H, 4.34; N, 8.08; Cl, 10.22. Found: C, 72.51; H, 4.25; N, 7.97; Cl, 9.99. [i] Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.17; H, 5.41; N, 7.52. Found: C, 74.28; H, 5.20; N, 7.44. [j] Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.18; H, 5.54; N, 8.06. [k] Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.16; H, 5.33; N, 8.10. [l] Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.04; H, 7.19; N, 9.51. [m] Anal. Calcd for $C_{22}H_{17}N_2OCl$: C, 73.22; H, 4.75; N, 7.76; Cl, 9.83. Found: C, 72.63; H, 4.99; N, 7.46; Cl, 10.54. [n] Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.65; H, 7.83; N, 8.67. [o] Anal. Calcd for $C_{21}H_{23}N_2O$: C, 79.21; H, 6.97; N, 8.80. Found: C, 79.37; H, 7.05; N, 8.95. [p] Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.05; H, 5.59; N, 7.93. [q] Anal. Calcd for $C_{21}H_{15}N_2OCl$: C, 72.72; H, 4.36; N, 8.08; Cl, 10.22. Found: C, 72.49; H, 4.64; N, 8.09; Cl, 10.12. [r] Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.95; H, 7.03; N, 9.46. [s] Reported,[24] mp 100-101 °C. [t] Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.66; N, 7.86. Found: C, 77.58; H, 5.90; N, 7.86. [u] Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.66; N, 7.86. Found: C, 77.26; H, 5.68; N, 7.71.

Table III. Yields and Physical Properties of 3

	R[d]	yield, %	mp, °C	NMR data (Me_2SO-d_6), δ
3a	C_6H_5	70	194 dec[a]	7.30 (m)
3b	m-ClC_6H_4	84	133 dec	7.10 (m)
3c	p-$MeOC_6H_4$	93	180 dec[b]	7.40 (m, 15 H), 3.40 (s, 3 H)
3d	$C_6H_5CH_2$	(49)[c]	liquid	

[a] Anal. Calcd for $C_{21}H_{17}BF_2N_2O$: C, 63.05; H, 4.28; N, 7.00. Found: C, 62.84; H, 4.47; N, 7.32. [b] Anal. Calcd for $C_{22}H_{19}BF_4N_2O_2$: C, 61.45; H, 4.45; N, 6.51. Found: C, 61.62; H, 4.59; N, 6.30. [c] Minimum yield, based on product formation in a 1,3-dipolar addition reaction with dimethyl acetylenedicarboxylate. [d] For all compounds R′ = R″ = C_6H_5.

therefore anticipated that such salts would undergo 1,3-dipolar addition reactions with suitable alkynes to give substituted pyrroles. This proved to be the case. For example, treatment of 5-imino-2,3,4-triphenyl-1,3-oxazolinium fluoroborate (3a) with dimethyl acetylenedicarboxylate at 110 °C for 12 h afforded dimethyl 1,2,5-triphenylpyrrole-3,4-dicarboxylate (8) in 80% yield (Scheme III). The compound was identical in all regards

Scheme III

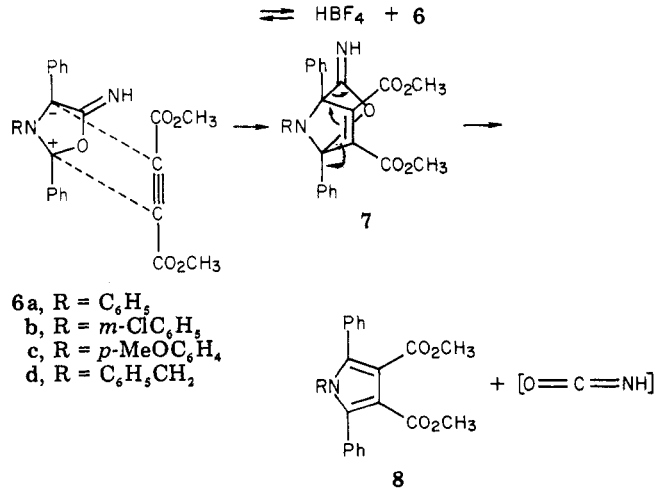

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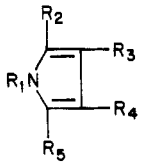
Table IV. Yields and Physical Properties of

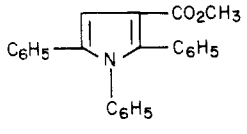


product[f]	R_1	R_2	R_3	R_4	yield, %	mp, °C	NMR data ($CDCl_3$), δ (J in Hz)
8a	C_6H_5	C_6H_5	CO_2Me	CO_2Me	80	197-200[a]	7.20 (m, 15 H), 3.70 (s, 6 H)
8b	*m*-ClC_6H_4	C_6H_5	CO_2Me	CO_2Me	73	173-174.5[b]	6.90 (m, 14 H), 3.68 (s, 6 H)
8c	*p*-$MeOC_6H_4$	C_6H_5	CO_2Me	CO_2Me	55	210-212[c]	7.20 (m, 10 H), 6.55 (q, 4 H), 3.60 (s, 3 H), 3.55 (s, 6 H)
9	C_6H_5	C_6H_5	CO_2Me	H	68	162-164[d]	7.10 (m, 16 H), 3.66 (s, 3 H)
14	H	C_6H_5CO	$CO_2C_2H_5$	H	75	214-215[e]	7.15 (m, 10 H), 6.82 (s, 1 H), 4.08 (q, 2 H, J = 7.2), 0.95 (t, 3 H, J = 7.2)

[a] Reported,[37] mp 196-197 °C. Spectra identical with that of an authentic sample of the compound provided by Professor J. W. Lown. Anal. Calcd for $C_{26}H_{21}NO_4$: C, 75.89; H, 5.15; N, 3.41. Found: C, 75.73; H, 5.45; N, 3.39. [b] Anal. Calcd for $C_{26}H_{20}ClNO_4$: C, 70.03; H, 4.52; N, 3.14. Found: C, 69.71; H, 4.78; N, 2.98. [c] Anal. Calcd for $C_{27}H_{23}NO_5$: C, 73.45; H, 5.25; N, 3.17. Found: C, 73.51; H, 5.14; N, 3.25. [d] Reported,[37] mp 152-157 °C. Anal. Calcd for $C_{24}H_{19}N_2O$: C, 81.56; H, 5.42; N, 3.92. Found: C, 81.25; H, 5.45; N, 3.83. [e] Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.07; H, 5.33; N, 4.34. [f] $R_5 = C_6H_5$ for all compounds.

(melting point and IR spectra) with a sample kindly furnished to us by Professor J. W. Lown.[37] It may be assumed, in analogy with the known reactions of Reissert salts,[21-23] that the mesoionic compound **6**, obtained by dissociation of **3a**, underwent a cycloaddition reaction with dimethyl acetylenedicarboxylate to give the adduct **7**, which subsequently eliminated isocyanic acid to provide **8**.

Dimethyl 1-(*m*-chlorophenyl)-2,5-diphenylpyrrole-3,4-dicarboxylate (**8b**), dimethyl 1-(*p*-methoxyphenyl)-2,5-diphenylpyrrole-3,4-dicarboxylate (**8c**), and dimethyl 1-benzyl-2,5-diphenyl-3,4-dicarboxylate (**8d**) were prepared in similar yields by cycloaddition reactions of dimethyl acetylenedicarboxylate with **6b**, **6c**, and **6d**, respectively. Also, reaction of **6a** with methyl propargylate, this time with refluxing in methanol solution, gave methyl 1,2,5-triphenylpyrrole-3-carboxylate (**9**). The properties of these compounds are provided in Table IV.



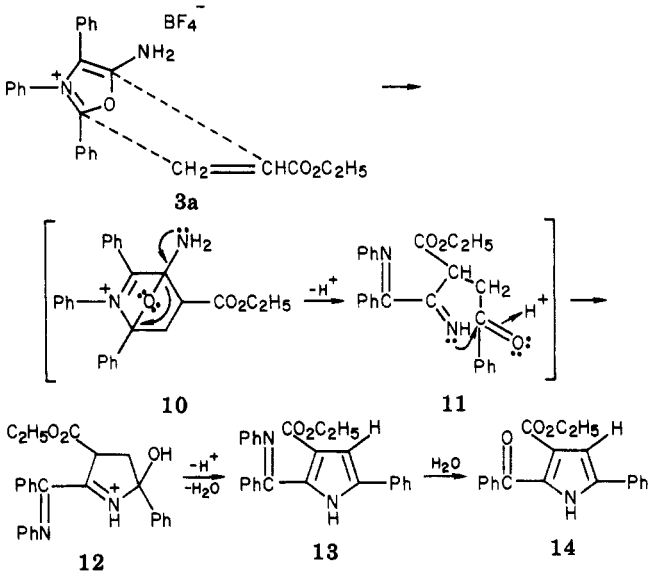
9

Evidence for the existence of tautomer **3a** in the salt derived from **2a** consists of the fact that treatment of the salt with ethyl acrylate in dimethylformamide for 12 h at 65 °C, with subsequent treatment with water, gives ethyl 2-benzoyl-5-phenylpyrrole-3-carboxylate (**14**) in 75% yield (Scheme IV).

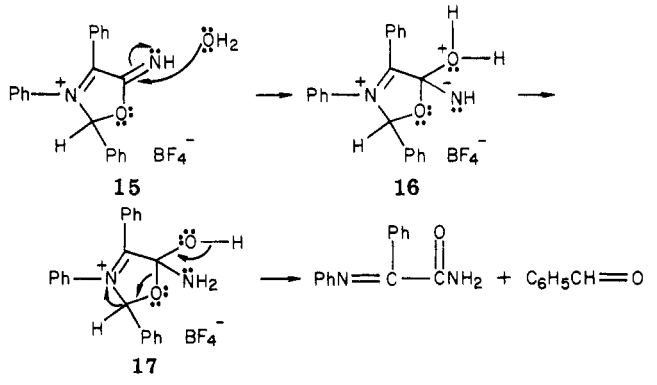
After acid-catalyzed hydrolysis of the Reissert salt **3a** with hydrochloric acid in dimethylformamide, a trace of benzaldehyde was detected, along with the major product, benzoic acid. In analogy with the chemistry of the quinoline and isoquinoline Reissert salts,[12-15] the formation of benzaldehyde represents evidence for the presence of compound **15** in the equilibrium mixture, since it would be difficult to write a mechanism for the formation of benzaldehyde involving any other tautomeric form of the salt.

Attack by a water molecule at the imido carbon in structure **15** leads, via intermediates **16** and **17**, to the formation of benzaldehyde plus an amide (Scheme V).

Scheme IV



Scheme V



The benzaldehyde was detected by its odor, and its presence was confirmed by isolation of its 2,4-dinitrophenylhydrazone. Benzoic acid is formed by dissociation of **3** to **2** and subsequent acid-catalyzed hydrolysis of the amide function of **2**.

Base-Catalyzed Reactions of Reissert Compounds. A Reissert analogue such as **2a** reacts with a strong base

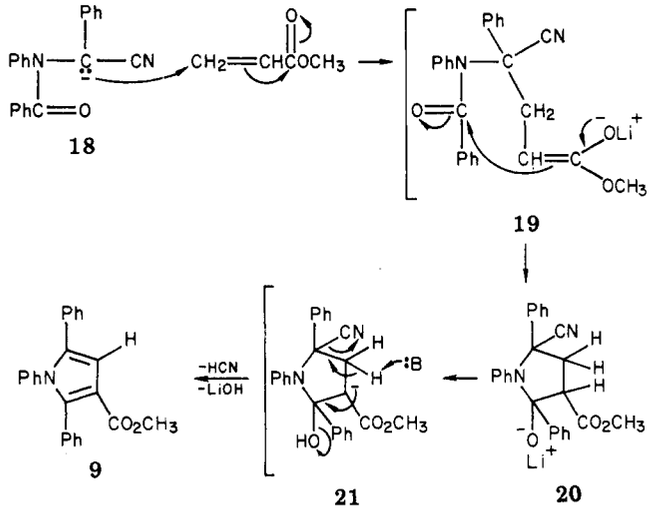
(37) Lown, J. W.; Matsumoto, K. *Can. J. Chem.* **1970**, *48*, 3406.

Table V. Syntheses, Properties, and Alkaline Cleavage Reactions of 22

	R′	R‴	yield, %	mp, °C	NMR data ($CDCl_3$), δ (J in Hz)	yield of 23, %
22a[l]	C_6H_5	$C_6H_5CH_2$	91	192-194[a]	7.25 (m, 20 H), 3.24 (s, 2 H)	64
b	p-ClC_6H_4	$C_6H_5CH_2$	100	176.5-177.5[b]	7.20 (m, 19 H), 3.15 (s, 2 H)	99
c	m-ClC_6H_4	$C_6H_5CH_2$	84	179-180[c]	7.16 (m, 19 H), 3.14 (s, 2 H)	93
d	o-ClC_6H_4	$C_6H_5CH_2$	78	195-196[d]	7.25 (m, 19 H), 3.96 (d, 1 H, J = 13), 2.74 (d, 1 H, J = 13)[e]	33
e	3,4-$(MeO)_2C_6H_3$	$C_6H_5CH_2$	83	165-166.5[f]	7.22 (m, 18 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.24 (br s, 2 H)	75
f	m-$MeOC_6H_4$	$C_6H_5CH_2$	77	152-154[g]	7.14 (m, 19 H), 3.65 (s, 3 H), 3.17 (s, 2 H)	64
g	o-$MeOC_6H_4$	$C_6H_5CH_2$	80	192-193[h]	7.10 (m, 19 H), 3.95 (s, 3 H), 3.80 (d, 1 H, J = 12.5), 2.92 (d, 1 H, J = 12.5)[e]	94
h	C_6H_5	n-C_4H_9	52	161-162[i]	7.45 (m, 15 H), 2.85 (m, 2 H), 0.91 (m, 7 H)	80
i	n-C_4H_9	$C_6H_5CH_2$	95	136-138[j]	7.25 (m, 15 H), 4.14 (d, 1 H, J = 13), 3.50 (d, 1 H, J = 13)	trace
j	C_6H_5	α-$C_{10}H_7CH_2$	100	195-197[k]	7.35 (m, 22 H), 3.70 (s, 2 H)	70

[a] Anal. Calcd for $C_{28}H_{22}N_2O$: C, 83.55; H, 5.51; N, 6.96. Found: C, 83.19; H, 5.54; N, 6.85. [b] Anal. Calcd for $C_{28}H_{21}ClN_2O$: C, 76.97; H, 4.84; N, 6.41; Cl, 8.11. Found: C, 77.14; H, 4.84; N, 6.55. [c] Anal. Calcd for $C_{28}H_{21}ClN_2O$: C, 76.97; H, 4.84; N, 6.41; Cl, 8.11. Found: C, 77.23; H, 4.91; N, 6.24; Cl, 8.26. [d] Anal. Calcd for $C_{28}H_{21}ClN_2O$: C, 76.97; H, 4.84; N, 6.41; Cl, 8.11. Found: C, 76.82; H, 5.02; N, 6.24; Cl, 8.29. [e] Diastereotopic splitting of CH_2. [f] Anal. Calcd for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.66; N, 6.06. Found: C, 77.69; H, 5.80; N, 6.04. [g] Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.26; H, 5.64; N, 6.40. [h] Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.72; H, 5.72; N, 6.43. [i] Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.56; N, 7.60. Found: C, 81.56; H, 6.72; N, 7.67. [j] Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.33. Found: C, 81.43; H, 7.02; N, 7.23. [k] Anal. Calcd for $C_{32}H_{24}N_2O$: C, 84.93; H, 5.34; N, 6.19. Found: C, 84.74; H, 5.62; N, 5.96. [l] R = R″ = C_6H_5 for all compounds.

Scheme VI



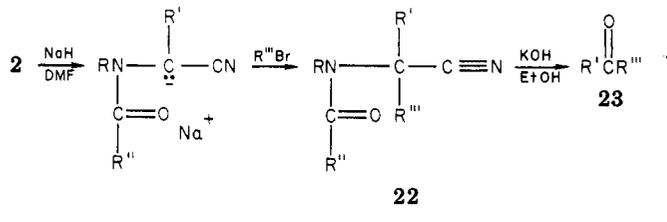
to form a deep red solution of the anion 18. The anion can be made to undergo nucleophilic addition or displacement reactions.

Phenyllithium was originally used to generate the anion 18 in tetrahydrofuran at −10 °C. Reaction of the anion with excess methyl acrylate in tetrahydrofuran gave the pyrrole 9 (Scheme VI), the same pyrrole obtained by the acid-catalyzed reaction of the Reissert analogue with methyl propargylate, in 48% yield.

Presumably, the mechanism involves an initial Michael-type addition of the Reissert anion to the methyl acrylate to give intermediate 19. An intramolecular nucleophilic addition of the resultant carbanionic center to the amide carbonyl carbon atom gives a five-membered-ring compound, 20, which subsequently eliminates the molecules of lithium hydroxide and hydrogen cyanide, as shown in 21.

In later work, it was found that the anion of an open-chain analogue of a Reissert compound could be generated more conveniently by the action of sodium hydride on 2

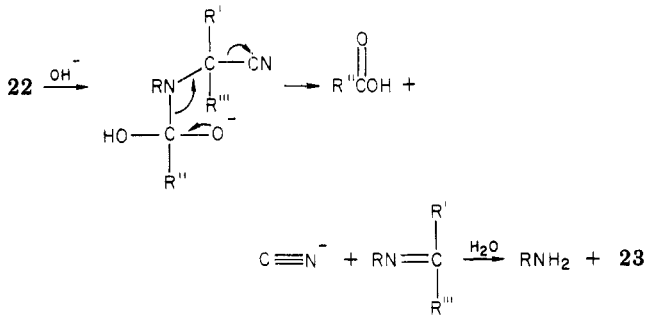
Scheme VII



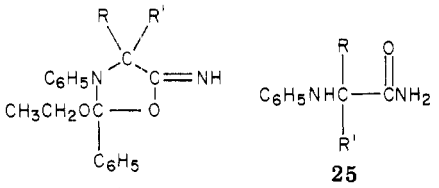
in dimethylformamide.[8] Reaction of the anion with a suitable alkyl bromide was found to give the alkylated product 22 (Scheme VII). Cleavage of 22 by the action of potassium hydroxide in ethanol solution was found to give the ketone 23. The results of several such sequences of reactions are given in Table V. The alkylated products, 22, have been characterized thoroughly by spectra and elemental analyses. The ketones, 23, are all known compounds and have been identified by physical properties, spectra, and the preparation of solid derivatives.

By analogy with the proposed[4,5] mechanism of base-catayzed cleavage of a conventional alkylated Reissert compound, it is believed that the conversion of 22 to 23 takes place by nucleophilic addition of a hydroxide ion to the carbonyl carbon atom of 22, elimination of a carboxylic acid and a cyanide ion, and subsequent hydrolysis of the residual Schiff base. An amine and a carboxylic acid are isolated in amounts equivalent to the ketone 23. When R is an aryl group, the conjugation in the incipient anil probably serves as a partial driving force for the cleavage reaction. This helps to explain why the cleavage reaction does not proceed well when R′ and R‴ are both alkyl groups. Treatment of 22 (R′ = n-C_4H_9 and R‴ = $C_6H_5CH_2$) with ethanolic potassium hydroxide gives 24 as the major product, only a trace amount of n-butyl benzyl ketone being obtained. It is also a well-known[38] phenomenon that the presence of *gem*-dialkyl substituents promotes the rate of ring closure to form a five-membered ring

(38) Capon, B. *Q. Rev., Chem. Soc.* **1964**, *18*, 45.



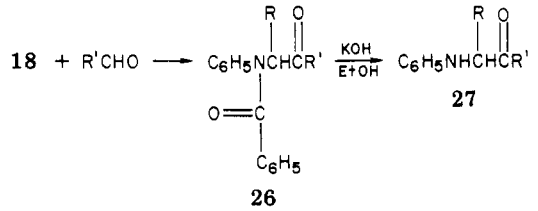
when this is possible. Furthermore, the presence of *gem*-dialkyl groups increases the thermodynamic stability of the ring form relative to the acyclic form. Alkaline hydrolysis of **24** under forcing conditions gives the amide **25**.



24 **25**

Although several of the ketones listed in Table V could readily be prepared in several simple steps from the fundamental starting materials, R'CHO and RBr, by other routes, others (e.g., *m*-chlorophenyl benzyl ketone, *o*-methoxyphenyl benzyl ketone, *m*-methoxyphenyl benzyl ketone, etc.) could not. Thus, the overall approach is of synthetic value, although not necessarily superior to similar methods making use of other acyl anion synthons.[39,40]

α-Anilino ketones **27** resulted when the anion **18** was caused to react with aldehydes, the initial reaction mixture being subjected to subsequent alkaline hydrolysis.



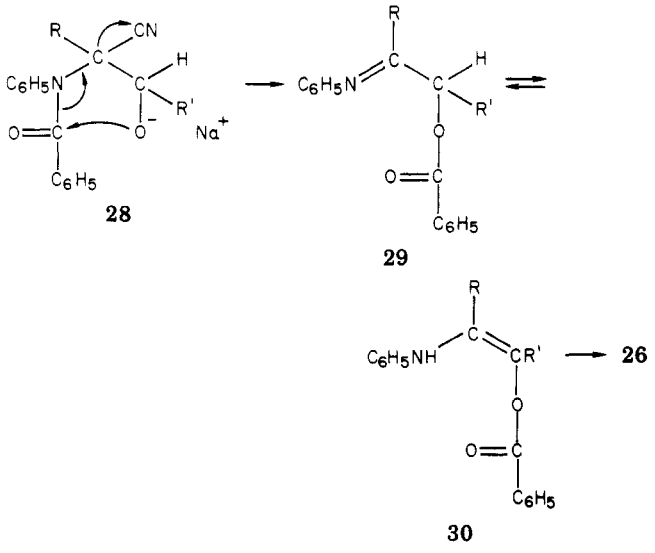
26 **27**

The results of several such reaction sequences are presented in Table VI. By limitation of the period of alkaline hydrolysis, it is possible to isolate the intermediate **26** from a mixture with **27**. Interconversion of **26** and **27** by alkaline hydrolysis and acylation, respectively, has been demonstrated.

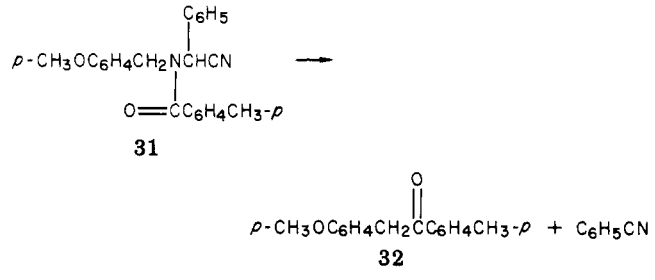
By analogy with the generally accepted mechanism of the reaction of conventional Reissert anions with aldehydes,[9] intermediates 28–30 (Scheme VIII) are tentatively suggested to be involved in the formation of **26** from **18** plus an aldehyde. However, it is conceivable that **26** could be formed directly from **28** without the intervention of **29** and **30**. On the other hand, N → O and O → N acyl migrations are known to occur readily.[42-46]

In a reaction which superficially appears to be somewhat reminiscent of the Stevens rearrangement,[47,51] **2** (R = benzyl, R' = R'' = phenyl) has been found to give desoxybenzoin (51%) when treated with sodium hydride in tetrahydrofuran. However, the fact the *p*-methoxybenzyl *p*-tolyl ketone (**32**) plus benzonitrile are obtained by treatment of **31** with sodium hydride in the same manner indicates that the mechanism of reaction is complex. The yield of the ketone **32** is 64%.

Scheme VIII



28 **29** **30**



31 **32**

The mechanism and scope of this reaction and of the reactions of the anions with aldehydes are under continuing investigation.

Experimental Section

Preparation of Aminonitriles 1. Each aminonitrile **1** was prepared by a three-step sequence of reactions from the starting aldehyde. For the aminonitriles derived from aromatic aldehydes, the first steps were the preparation of the cyanohydrin via the sodium bisulfite adduct by the general method of Corson et al.[52] Each crude cyanohydrin was dissolved in absolute ethanol and refluxed overnight in the presence of an equivalent amount of the appropriate primary amine. Usually, the aminonitrile **1** crystalized when the solution was cooled. Purification of each aminonitrile was effected by recrystallization from aqueous ethanol.

Each aminonitrile **1** exhibited a sharp peak in its IR spectrum at about 3350 cm^{-1}, owing to the presence of the NH group. Each NMR spectrum displayed two sets of doublets arising from coupling of the adjacent CH and NH groups. Following an exchange reaction with deuterium oxide, the NH absorption disappeared, and the CH absorption became a singlet. Other physical data are provided in Table I.

In the preparation of the aminonitrile **11** derived from *n*-valeraldehyde, the procedure of Taylor and Hauser[53] was utilized.

(39) Lever, O. W., Jr. *Tetrahedron* **1976**, *32*, 1943.
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(41) Phillips, A. P.; Baltzly, A. *J. Am. Chem. Soc.* **1947**, *69*, 200.
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(47) Stevens, T. S. *J. Chem. Soc.* **1930**, 2107.
(48) Thomson, T.; Stevens, T. S. *J. Chem. Soc.* **1932**, 55.
(49) Julian, P. L.; Meyer, E. W.; Magnani, A.; Cole, W. *J. Am. Chem. Soc.* **1945**, *67*, 1203.
(50) Ogato, Y.; Kawasaki, A. *J. Chem. Soc., Perkin Trans. 2* **1971**, 325.
(51) Cowper, R. M.; Stevens, T. S. *J. Chem. Soc.* **1947**, 1041.
(52) Corson, B. B.; Dodge, R. A.; Harris, S. A.; Yeaw, J. S. "Organic Synthesis"; Wiley: New York, 1932; Collect. Vol. I, p 336.

Table VI. Syntheses and Physical Properties of 26 and 27

	R	R′	mp, °C		yield,[a] %	mp, °C	NMR data ($CDCl_3$) for 27, δ (J in Hz)
26a	C_6H_5	C_6H_5	148.5-150[b]	27a	61	98-99[c]	
b	C_6H_5	p-ClC_6H_4	114-116[d]	b	53	153-154[e]	7.3 (m, 14 H), 5.3 (d, 1 H, J = 7), 5.9 (d, 1 H, J = 7)
c	C_6H_5	p-$MeOC_6H_4$		c	45	143-144[f]	7.35 (m, 14 H), 6.0 (ds, 1 H), 5.35 (ds, 1 H), 3.65 (s, 3 H)
d	p-ClC_6H_4	p-$MeOC_6H_4$	130-131[g]	d	50	143-144[h]	7.35 (m, 13 H), 5.9 (d, 1 H, J = 7), 3.85 (s, 3 H)

[a] Based on 2. [b] Anal. Calcd for $C_{26}H_{21}NO$: C, 82.83; H, 5.42; N, 3.58. Found: C, 82.73; H, 5.77; N, 3.45. [c] Reported,[51] mp, 101-102 °C. [d] Anal. Calcd for $C_{27}H_{20}N_2ClO_2$: C, 76.12; H, 4.74; N, 3.29; Cl, 8.33. Found: C, 76.23; H, 4.97; N, 3.18; Cl, 8.39. [e] Reported,[51] mp 154 °C. [f] Reported,[51] mp 143 °C. [g] Structure based on IR data and analogy. [h] Anal. Calcd for $C_{21}H_{18}NClO_2$: C, 71.69; H, 5.16; N, 3.98; Cl, 10.08. Found: C, 71.89; H, 5.29; N, 3.73; Cl, 10.34.

The product was purified by sublimation in vacuo.

Preparation of Reissert Analogues 2. Each Reissert analogue 2 was prepared by dissolving the aminonitrile 1 in anhydrous pyridine, with subsequent addition at 0 °C of benzoyl chloride. The reaction mixture was generally allowed to stir overnight at room temperature, but, in some instances, a reaction period of but 4 h provided a good yield of 2. Each reaction mixture was poured into ice-cold water and stirred vigorously. The Reissert analogue 2 usually solidified at this point and was collected by filtration. However, if solidification did not occur, the mixture was extracted with ether or methylene chloride, and the extract was washed successively with dilute hydrochloric acid, water, dilute sodium hydroxide solution, and water again. Evaporation of the solvent left an oil which was induced to crystallize from aqueous ethanol. Each Reissert analogue was purified by recrystallization from aqueous ethanol.

The infrared spectrum of each Reissert analogue exhibited a strong amide carbonyl absorption peak at about 1645 cm^{-1}. Other physical data are provided in Table II.

Alkylation of 2. Each Reissert analogue 2 was dissolved in anhydrous DMF and added to an equivalent amount of sodium hydride, the mixture being maintained under a nitrogen atmosphere. To the bright red solution of the anion of 2 was added an equivalent amount of alkyl halide. When benzyl bromide was used, the S_N2 reaction occurred rapidly, as evidenced by an almost immediate change in the color of the solution from red to yellow. With n-butyl bromide, a reaction period of about 2.5 days was required. With α-(chloromethyl)naphthalene, a 4-day reaction period was necessary to bring about discharge of the red color. Workup consisted of pouring the reaction mixture into ice-cold water, stirring, and collecting the precipitate which had formed. Each compound was purified by recrystallization from aqueous ethanol.

The infrared spectrum of each alkylated compound, 22, exhibited a strong amide carbonyl absorption at about 1665 cm^{-1}. Diastereotopic splitting of the benzylic protons was evident in the NMR spectra of all the benzylated compounds. The splitting ranged from a broadened singlet to a distinct pair of doublets for the various compounds 22 (R‴ = benzyl). Additional physical data for these compounds are provided in Table V.

Alkaline Cleavage of 22. A solution of 0.008 mol of each alkylated Reissert analogue 22 in 30 mL of 95% ethanol was mixed with a solution of 0.08 mol of potassium hydroxide in 5 mL of water. Reflux time ranged from 5 to 48 h. The solution was concentrated to dryness in vacuo, and the residue was dissolved in equal amounts of water and methylene chloride. The methylene chloride solution was washed with 10% hydrochloric acid. The ketone 23 was obtained on evaporation of the methylene chloride solution. All of the ketones listed in Table V are known compounds, and the identity of each ketone was established by melting point and mixture melting point with an authentic sample. Also, comparisons of IR and NMR spectra confirmed the identity. Benzoic acid was obtained by acidification of the aqueous layer from the methylene chloride extraction, and aniline was obtained by treatment of the hydrochloric acid wash solution with sodium hydroxide solution.

(53) Taylor, H. M.; Hauser, C. R. "Organic Synthesis"; Wiley: New York, 1973; Collect. Vol. V, p 25.

Preparation of Hydrofluoroborate Salts 3. To a solution of 0.02 mol of each Reissert analogue in 200 mL of acetic acid was added dropwise 4.0 mL of 48% fluoroboric acid. The solution was stirred for 30 min and then poured into 1 L of anhydrous ether. The pale yellow solid which precipitated was collected by filtration and washed with fresh ether.

The IR spectrum (KBr pellet) of each salt 3 exhibited a broad absorption peak at 3310–3350 cm^{-1} (NH_2). Additional data for these compounds are provided in Table III.

Reactions of 3 with Dimethyl Acetylenedicarboxylate. A mixture of 0.005 mol of each salt 3 with 7.5 mL (0.06 mol) of dimethyl acetylenedicarboxylate was heated at 110 °C for 10 h. The cooled solution was mixed with methylene chloride, and the solid which had formed was removed by filtration. Evaporation of the filtrate left an oil which was induced to crystallize from aqueous ethanol. Recrystallization from aqueous ethanol afforded the pure substituted pyrroles 8. The IR spectrum (KBr pellet) of each of these compounds exhibited an ester carbonyl peak at 1700–1710 cm^{-1}. Additional data for the pyrroles are provided in Table IV.

Preparation of Ethyl 2-Benzoyl-5-phenylpyrrole-3-carboxylate (14). To a solution of 2.0 g (0.005 mol) of the hydrofluoroborate salt 3a in 10 mL of DMF maintained at 65 °C was added 2.0 mL of ethyl acrylate. The mixture was heated at 65 °C for 10 h and poured into ice-cold water, and the hydrolysate was made slightly basic with ammonium hydroxide solution and extracted with methylene chloride. Evaporation of the solvent left an oil which was induced to crystallize from aqueous ethanol. The pyrrole 14 was purified by recrystallization from ethyl acetate; yield 1.2 g (75%). Additional data are provided in Table IV.

Methyl 1,2,5-Triphenylpyrrole-3-carboxylate (9). Procedure A. To a solution of 2.00 g (0.005 mol) of 3a in 25 mL of absolute ethanol was added 2.00 g (0.02 mol) of methyl propargylate, and the solution was heated at 70 °C for 10 h. The solution was evaporated to dryness, and methylene chloride was added to the residue. The mixture was filtered, and the filtrate was evaporated to give a solid. This was crystallized from ethanol to give 1.20 g (68%) of the pyrrole 9. The infrared spectrum (KBr, pellet) of 9 exhibited a carbonyl absorption peak at 1710 cm^{-1}. Additional data for the compound are provided in Table IV.

Procedure B. To an ice-cooled solution of 6.28 g (0.02 mol) of 2a in 100 mL of anhydrous dioxane was added 11.5 mL of a 1.75 N solution of phenyllithium in THF. To the resulting dark red solution was added a solution of 5.4 mL of methyl acrylate in 20 mL of THF. The solution was stirred at room temperature for 10 h, poured into water, and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent provided an oil, which was dissolved in 250 mL of toluene. p-Toluenesulfonic acid (0.25 g) was added and the solution refluxed for 10 h. The toluene solution was washed with water and then concentrated to dryness. The residual oil was induced to crystallize from ethanol to give 3.4 g (48%) of the pyrrole 9.

Preparation of α-Anilino Ketones 27. A solution of 0.02 mol of each Reissert analogue 2 in 100 mL of anhydrous THF was treated with 2 equiv of sodium hydride. Then a solution of 0.02 mol of the appropriate aldehyde in 25 mL of THF was added to the red solution of the anion, and the mixture was stirred at room temperature for 8–24 h, until the red color had been discharged. After removal of the solvent in vacuo, the residue was mixed with

50 mL of water and 100 mL of ethanol, and the solution was refluxed for 24 h. Each anilino ketone **27** precipitated when the solution was cooled. Purification of each anilino ketone was effected by crystallization from 95% ethanol.

Each anilino ketone **27** exhibited sharp peaks at about 3350 cm^{-1} (NH) and at about 3350 cm^{-1} (carbonyl) in its IR spectrum. Additional data are provided in Table VI.

Isolation of Ketoamides 26. The same procedure was followed as in the preparation of **27**, except that the period of reflux after the addition of water and ethanol was limited to 2 h. When the solution was cooled, each ketoamide **26** precipitated. Each was purified by crystallization from 95% ethanol.

The IR spectrum of each ketoamide exhibited two sharp carbonyl peaks at about 1690 and 1645 cm^{-1}. Additional data are provided in Table IV.

Rearrangement of 2 (R = Benzyl). A solution of 0.04 mol of **2** (R = benzyl) in 100–200 mL of THF was treated with 2 equiv of sodium hydride. The initially deep red solution was refluxed for 12 h and the solution was concentrated to dryness in vacuo. The yellow residue was dissolved in 50 mL of concentrated hydrochloric acid and 100 mL of ethanol, and the solution was refluxed for 24 h. Each desoxybenzoin crystallized when the solution was cooled and was recrystallized from 95% ethanol. Each desoxybenzoin was identified by comparison (melting point, mixture melting point, IR spectrum, and NMR spectrum) with an authentic sample of the desoxybenzoin.

Registry No. **1a**, 4553-59-7; **1b**, 15190-65-5; **1c**, 32323-74-3; **1d**, 32153-18-7; **1f**, 32377-36-9; **1g**, 72867-29-9; **1h**, 72881-52-8; **1i**, 54840-97-0; **1j**, 72867-30-2; **1k**, 72867-31-3; **1l**, 72867-32-4; **1m**, 72867-33-5; **1o**, 39640-73-8; **1p**, 32377-38-1; **1q**, 4686-05-9; **1r**, 72867-34-6; **2a**, 14062-91-0; **2b**, 72867-35-7; **2c**, 72867-36-8; **2d**, 5367-12-4; **2e**, 30057-98-8; **2f**, 72867-37-9; **2g**, 72867-38-0; **2h**, 72867-39-1; **2i**, 72867-40-4; **2j**, 72867-41-5; **2k**, 72867-42-6; **2l**, 72867-43-7; **2m**, 72867-44-8; **2n**, 72867-45-9; **2o**, 72867-46-0; **2p**, 72867-47-1; **2q**, 72867-44-8; **2r**, 72867-48-2; **2s**, 14101-08-7; **2t**, 72867-49-3; **2u**, 72867-50-6; **3a**, 72867-52-8; **3b**, 72867-54-0; **3c**, 72867-56-2; **3d**, 72867-58-4; **8a**, 30082-50-9; **8b**, 72867-59-5; **8c**, 72867-60-8; **9**, 30082-52-1; **14**, 72867-61-9; **22a**, 72867-62-0; **22b**, 72867-63-1; **22c**, 72867-64-2; **22d**, 72867-65-3; **22e**, 72867-66-4; **22f**, 72867-67-5; **22g**, 72867-68-6; **22h**, 72867-69-7; **22i**, 72867-70-0; **22j**, 72867-71-1; **23a**, 451-40-1; **23b**, 1889-71-0; **23c**, 62482-45-5; **23d**, 72867-72-2; **23e**, 3141-93-3; **23f**, 62381-24-2; **23g**, 33470-10-9; **23h**, 1009-14-9; **23j**, 16216-08-3; **26a**, 7714-86-5; **26b**, 72867-73-3; **26d**, 72881-53-9; **27a**, 5722-91-8; **27b**, 72867-74-4; **27c**, 6910-79-8; **27d**, 72867-75-5; $C_6H_5NH_2$, 62-53-3; *m*-$ClC_6H_4NH_2$, 108-42-9; *p*-$MeOC_6H_4NH_2$, 104-94-9; $C_6H_5CH_2NH_2$, 100-46-9; *p*-$ClC_6H_4CH_2NH_2$, 104-86-9; *n*-$C_5H_{11}NH_2$, 110-58-7; c-$C_6H_{11}NH_2$, 108-91-8; *m*-$MeOC_6H_4NH_2$, 536-90-3; *p*-$ClC_6H_4NH_2$, 106-47-8; 2,4,6-$(Me)_3C_6H_2NH_2$, 88-05-1; C_6H_5CHO, 100-52-7; HCHO, 50-00-0; *p*-ClC_6H_4CHO, 104-88-1; *m*-ClC_6H_4CHO, 587-04-2; *o*-ClC_6H_4CHO, 89-98-5; 3,4-$(MeO)_2C_6H_3CHO$, 120-14-9; *m*-$MeOC_6H_4CHO$, 591-31-1; *o*-$MeOC_6H_4CHO$, 135-02-4; *n*-C_4H_9CHO, 110-62-3; $C_6H_5CH(OH)CN$, 532-28-5; $HOCH_2CN$, 107-16-4; *p*-$ClC_6H_4CH(OH)CN$, 13312-83-9; *m*-$ClC_6H_4CH(OH)CN$, 53313-92-1; *o*-$ClC_6H_4CH(OH)CN$, 13312-84-0; 3,4-$(MeO)_2C_6H_3CH(OH)CN$, 6309-18-8; *m*-$MeOC_6H_4CH(OH)CN$, 53313-94-3; *o*-$MeOC_6H_4CH(OH)CN$, 53313-93-2; *n*-$C_4H_9CH(OH)CN$, 64350-07-8; C_6H_5COCl, 98-88-4; CH_3COCl, 75-36-5; *p*-$MeOC_6H_4CHO$, 123-11-5; dimethyl acetylenedicarboxylate, 762-42-5; ethyl acrylate, 140-88-5; methyl propargylate, 922-67-8; methyl acrylate, 96-33-3.

Notes

Reductive Methylation of Polycyclic Aromatic Quinones

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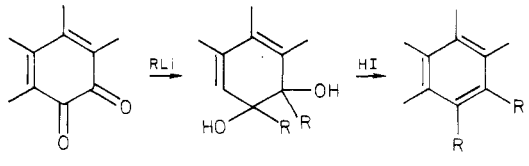
Introduction of methyl groups into appropriate molecular regions of polycyclic aromatic hydrocarbons can profoundly influence their carcinogenic activity.[1-3] In connection with studies directed toward determining the effects of methyl substitution on metabolic activation of carcinogenic hydrocarbons, we required a series of *o*- and *p*-dimethyl-substituted hydrocarbons. For this purpose, we developed a convenient synthetic approach involving reaction of the related quinones with methyllithium followed by reduction of the resulting dimethyl dihydro diols with HI in acetic acid:[4]



Results are summarized in Table I. Reactions with methyllithium were carried out in ether at room temperature. The NMR spectra of the crude dimethyl dihydro diols, which were employed directly in the subsequent step, were consistent with proposed structures. The overall yields of the dimethylarenes were generally high.

The only difficulty experienced was the tendency of certain dimethylarenes to undergo further hydrogenation of the dimethyl-substituted ring to furnish the related dihydro derivatives. In the case of chrysene-5,6-dione, the optimum yield of 5,6-dimethylchrysene (**4**) was obtained with short reaction time (5 min). Reactions conducted for longer periods or in the presence of phosphorus[4] afforded substantial amounts of 5,6-dimethyl-5,6-dihydrochrysene. In contrast, the analogous dimethyl derivatives of phenanthrene (**1**), benzo[*a*]pyrene (**2**), 7-methylbenzo[*a*]pyrene (**3**), and dibenz[*a*,*c*]anthracene (**5**) proved relatively insensitive to conditions; reductions carried out overnight (20 h) or in the presence of phosphorus gave no evidence of the formation of the corresponding dimethyldihydroarenes. In the case of benz[*a*]anthracene-7,12-dione, a precipitate which formed initially on combination of the reactants was identified as 7-iodomethyl-12-methylbenz[*a*]anthracene (**6a**). The latter dissolved rapidly on warming, with efficient conversion to 7,12-dimethylbenz[*a*]anthracene (**6b**). Like **4**, **6b** exhibited a propensity to

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(4) Efficient reduction of polycyclic quinones to fully aromatic hydrocarbons with HI in acetic acid has also recently been described. Phosphorus has been shown in these studies to promote hydrogenation of polyarenes: Konieczny, M.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 4813.

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