Reissert Compound Studies. Cyclization of *N*-(ω-Chloroalkanoyl)Reissert Compounds (1)

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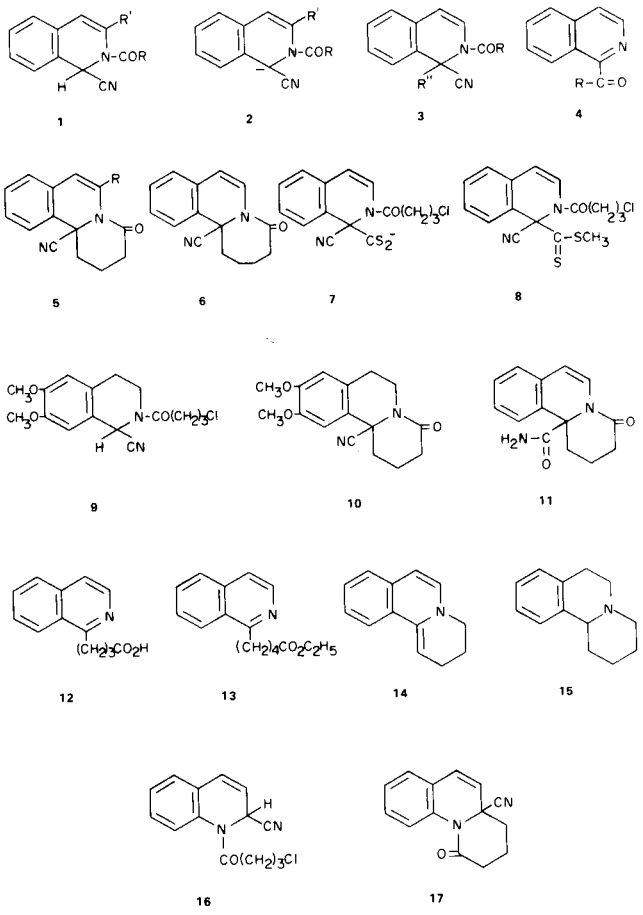
Treatment of 2-(4-chlorobutanoyl)- and 2-(5-chloropentanoyl)-1,2-dihydroisoquinaldonitrile with sodium hydride gave rise to tricyclic benzoquinolizone and azepino[1,2-*a*]isoquinoline derivatives. A similar reaction was observed in the quinoline series. Several reactions of 1,2,3,4-tetrahydro-4-oxo-11b*H*-benzo[*a*]quinolizine-11b-carbonitrile are reported.

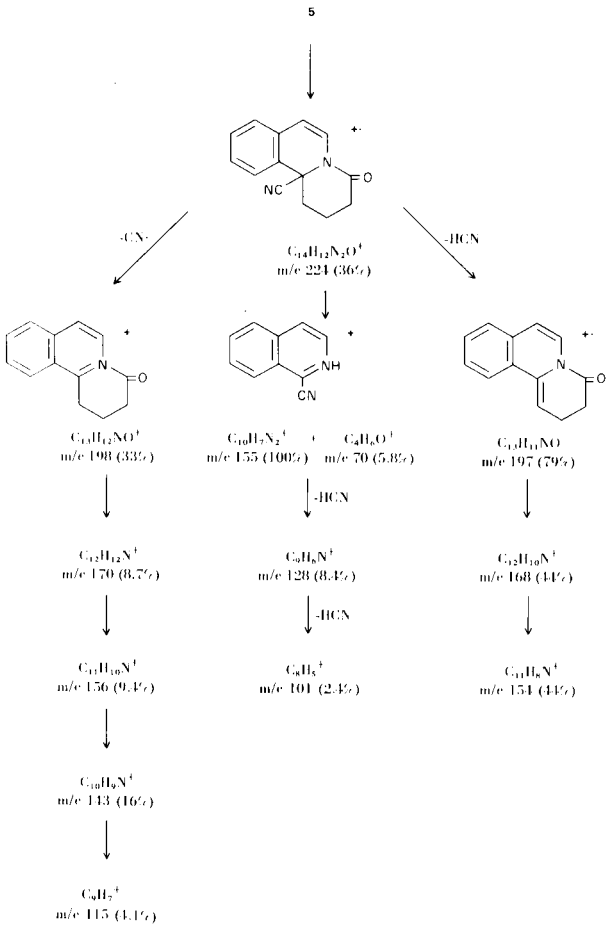
A wide variety of reactions has been reported (4) for Reissert compounds (*N*-acyl-1,2-dihydroquinaldonitriles and *N*-acyl-1,2-dihydroisoquinaldonitriles). Among the most useful synthetic reactions of Reissert compounds are those carried out in the presence of a strong base. Treatment of the Reissert compound from isoquinoline (**1**, R′ = H) with sodium hydride in dimethylformamide at room temperature gives the anion (**2**, R′ = H) (5). In the presence of an alkyl halide this anion gives the alkylated Reissert compound **3** while in the absence of any added reactant the rearrangement product **4** is obtained.

In order to study the competition between alkylation and rearrangement, and in hopes of preparing novel tricyclic systems we have studied the reaction of a series of *N*-(ω-chloroalkanoyl)Reissert compounds with sodium hydride in dimethylformamide. Treatment of **1** (R = $CH_2CH_2CH_2Cl$, R′ = H) with sodium hydride in dimethylformamide led to alkylation and the isolation of the lactam **5** (R = H) (6). In a similar manner the 3-methyl analogue of **1** (R = $CH_2CH_2CH_2Cl$, R′ = CH_3) gave **5** (R = CH_3). Extension of this reaction to **1** (R = CH_2CH_2-CH_2CH_2Cl, R′ = H) gave the 7-membered ring compound 2,3,4,5-tetrahydro-5-oxoazepino[2,1-*a*]isoquinoline-12b-(1*H*)carbonitrile (**6**); however, no cyclization product could be obtained from **1** (R = CH_2CH_2Cl, R′ = H or R = $CH_2CH_2CH_2CH_2CH_2Br$, R′ = H).

The cyclization of **1** (R = $CH_2CH_2CH_2Cl$, R′ = H) to the 6-membered ring is quite rapid and occurs even in the presence of two equivalents of isopropyl iodide. Reaction of the anion **2** (R = $CH_2CH_2CH_2Cl$, R′ = H) with carbon disulfide, however, led to a 90% recovery of **1** (R = $CH_2CH_2CH_2Cl$, R′ = H) indicating formation of the



SCHEME 1



dithiocarboxylate anion **7** (red orange) but that if failed to displace the chlorine (5). This was confirmed by the isolation of **8** in quantitative yield when the reaction was carried out in the presence of methyl iodide.

Application of this cyclization reaction to dihydro derivatives of Reissert compounds (7,8) seemed to offer useful synthetic extensions. When treated with sodium hydride **9** gave a 99% yield of the expected **10**.

A number of reactions of the novel tricyclic system **5** (R = H) were studied. Oxidation of **5** (R = H) with alkaline hydrogen peroxide gave rise to **11**. Hydrolysis of **5** (R = H) which either acid or base gave rise to **12**, while the ethyl ester of **12** was obtained when **5** (R = H) was refluxed in ethanol. The ester **13** was similarly obtained by refluxing **6** in ethanol. The fact that **11** was recovered unchanged from refluxing ethanol indicates the importance of the elimination of cyanide in this solvolytic ring opening. Reduction of **5** (R = H) with lithium aluminum hydride apparently resulted in loss of hydrogen cyanide (9) to give **14** as its hydrobromide. Catalytic hydrogenation of **14** gave **15** whose picrate had the same melting point as reported (10) for **15** picrate prepared by another route.

The cyclization reaction was extended to the quinoline series by treatment of the crude Reissert compound **16** with sodium hydride to give the tricyclic compound **17**. The spectral evidence is consistent with structure **17** as opposed to alkylation in the 4-position as has been reported (4) for quinoline Reissert compounds.

The high resolution mass spectra of **5**, (R = H), **11**, **14**, and **17** confirm the structures assigned and deserve some comment (11). The major fragmentation product of **5** (R = H), as shown in Scheme 1, involved the loss of ring C to give the ion m/e 155. The other fragmentation pathways involved the loss of a cyano radical and of HCN. The loss of a 1-alkyl group and of the substituent on nitrogen prior to the loss of cyanide has been previously observed (12) in the mass spectra of Reissert compounds. Further fragmentation of **5** (R = H) include: [198 → 170 (8.7%) → 156 (9.4%) → 143 (16%) → 115 (4.1%); 155 → 128 (8.4%) → 101 (2.4%); 197 → 168 (44%) → 154 (44%)]. The quinoline analogue **17** exhibited the same fragmentation pathways as **5**: [224 (29%) → 155 (100%) → 128 (9%) → 101 (2.4%); 224 → 197 (17%) → 168 (12%) → 154 (22%) → 128; 224 → 198 (21%) → 170 (13%) → 143 (35%) → 115 (4%)]. In the case of **11** no molecular ion was observed [$C_{14}H_{14}N_2O_2$, m/e 242 (0.15%)] because of the very favorable fragmentation involving loss of $CONH_2$ to give the ion $C_{13}H_{12}NO$, m/e 198 (100%) which fragmented in the same manner as shown in Scheme 1 [198 → 170 (32%) → 143 (13%) → 115 (5%)]. The mass spectrum of **11** did not show any evidence for a fragmentation path analogous to the favored 224 → 155 path exhibited by **5** (R = H) and **17**. Although **11** did not exhibit a molecular ion in its high resolution mass spectrum, it did exhibit a very intense $(M + H)^+$ ion (m/e 243) in its chemical ionization (isobutane) mass spectrum. Compound **14** also exhibited an intense $(M + H)^+$ ion (m/e 184) in its chemical ionization (isobutane) mass spectrum. The major fragmentation pathways of **14** resemble the fragmentation of the ion m/e 198 and 197 shown in Scheme 1: [183 (59%) → 182 (38%) → 170 (12%) → 143 (13%) → 115 (4.7%); 183 → 168 (9%) → 154 (16%)].

EXPERIMENTAL (13)

Preparation of Reissert Compounds.

Several of the Reissert compounds used in this work had been previously reported (14). The remaining compounds were prepared by the standard methylene chloride-water procedure (15). 2-(3-Chlorobutanoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**1**, R = $(CH_2)_3Cl$, R' = CH_3) was prepared in 27% yield, m.p. 69-72° (ethanol), ir (potassium bromide): 1670 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; N, 10.20. Found: C, 65.25; H, 5.37; N, 10.15.

2-(3-Chlorobutanoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitrile (**9**).

This compound was prepared in 30% yield, m.p. 158-159° (ethyl acetate-hexane); ir (potassium bromide): 1653 cm^{-1}.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_3$: C, 59.53; H, 5.93; N, 8.68. Found: C, 59.50; H, 6.00; N, 8.48.

2-(6-Bromohexanoyl)-1,2-dihydroisoquinaldonitrile (**1**, R = $(CH_2)_5$ Br, R′ = H).

This compound was prepared in 56% yield, m.p. 95-96° (ethanol); ir (potassium bromide): 1675 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}BrN_2O$: C, 56.67; H, 5.14. Found: C, 57.85; H, 5.16.

1,2,3,4-Tetrahydro-4-oxo-11b*H*-benzo[*a*]quinolizine-11b-carbonitrile (**5**, R = H).

To a solution of 5.61 g. (0.0215 mole) of **1** (R = $(CH_2)_3Cl$, R′ = H) in 90 ml. of dimethylformamide was added with stirring 1.00 g. (0.0215 mole) of 50% sodium hydride in mineral oil. The mixture was stirred at room temperature for 1.5 hours, filtered, and the filtrate poured onto ice. The solid product was isolated by filtration and recrystallized from ethanol or ethyl acetate-hexane to give 4.25 g. (88%) of **5** (R = H), m.p. 136-138°; ir (potassium bromide): 1670 cm^{-1}; nmr (deuteriochloroform): 2.17-3.10 (m, 6), 6.23 (d, 1, J = 8), 7.29 δ (m, 5).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.19; H, 5.44; N, 12.54.

When this reaction was carried out in the presence of carbon disulfide and methyl iodide (5) a quantitative yield of **8**, m.p. 136-138° (ethanol); nmr (deuteriochloroform): 2.16 (t, 2, J = 6), 2.53 (s, 3), 2.4-3.0 (m, 2), 3.61 (t, 2, J = 6), 5.81 (d, 1, J = 8), 6.92 (d, 1, J = 8), 6.7-7.6 (m, 3), 7.7-8.0 δ (m, 1) was obtained.

Anal. Calcd. for $C_{16}H_{15}ClN_2OS_2$: C, 54.76; H, 4.31; N, 7.99. Found: C, 54.74; H, 4.47; N, 7.98.

2,3,4,5-Tetrahydro-5-oxo-azepino[2,1-*a*]isoquinoline-12b(1*H*)carbonitrile (**6**).

Using the procedure described above **1** (R = $(CH_2)_4Cl$, R′ = H) gave a 72% yield of **6**, m.p. 91-92° (petroleum ether); ir (potassium bromide): 2230 (w), 1673 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.68; H, 5.77; N, 11.73.

6-Methyl-1,2,3,4-tetrahydro-4-oxo-11b*H*-benzo[*a*]quinolizine-11b-carbonitrile (**5**, R = CH_3).

Using the procedure described above **1** (R = $(CH_2)_3Cl$, R′ = CH_3) gave an 86% yield of **5** (R = CH_3), m.p. 124-126° (ethyl acetate-hexane); nmr (deuteriochloroform): 2.3 (m, 6), 2.36 (d, 3, J = 1), 6.28 (q, 1, J = 1), 7.20 δ (s, 4).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.87; H, 6.01; N, 11.89.

9,10-Dimethoxy-1,2,3,4,6,7-hexanhydro-4-oxo-11b*H*-benzo[*a*]-quinolizine-11b-carbonitrile (**10**).

Using the procedure described above **9** gave a 40% yield (after chromatography) of **10**, m.p. 109-110° (hexane-methylene chloride); nmr (deuteriochloroform): 1.5-3.2 (m, 8), 3.85 (s, 6), 4.85 (m, 2), 6.60 (s, 1), 6.80 δ (s, 1).

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.20; H, 6.21; N, 9.85.

1,2,3,4-Tetrahydro-1-oxo-4a*H*-benzo[*c*]quinolizine-4a-carbonitrile (**17**).

Reaction of quinoline, potassium cyanide, and 4-chlorobutanoyl chloride under a variety of conditions failed to yield a crystalline Reissert compound. The oil obtained using the methylene chloride-water method (15) was chromatographed on alumina (chloroform) to give an oil **16** (ir: 1670 cm^{-1}) that was reacted as described above with sodium hydride in dimethylformamide. A 15% yield (after chromatography) of **17**, m.p. 142-143° (ethanol); ir (potassium bromide): 2240 (w), 1670 cm^{-1}; nmr (deuteriochloroform): 6.77 (d, 1, J = 9), 5.82 (d, 1, J = 9), 7.1-8.0 (m, 4), 1.83-2.85 δ (m, 6) was obtained.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.76; H, 5.48; N, 12.58.

Oxidation of **5** (R = H).

A suspension of 2.24 g. (0.01 mole) of **5** (R = H) in 30 ml. of water containing 3.10 g. of 50% hydrogen peroxide was stirred while 2.86 g. of 25% potassium hydroxide was added. The mixture was heated at 45° for 15 minutes and 55° for 30 minutes. After cooling, filtration gave 1.74 g. (72%) of **11**, m.p. 266-268° (chloroform); ir (potassium bromide): 3395, 3160, 1680, 1640 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.19; H, 5.72; N, 11.47.

Hydrolysis of **5** (R = H) and **6**.

A solution of 1.0 g. (0.0045 mole) of **5** (R = H) and 0.72 g. of potassium hydroxide in 6 ml. of 50% aqueous ethanol was refluxed for 30 minutes, poured onto 25 g. of ice and filtered (trace). The filtrate was washed with ether, made neutral with hydrochloric acid and extracted with ether. Concentration of the ether gave 0.42 g. (44%) of 4-(1-isoquinolyl)butyric acid **12**, m.p. 130-131° (ether) (reported (16), m.p. 126°); ir (potassium bromide): 2415, 1680, 1270 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.58; H, 6.16.

The same acid (**12**) was obtained in 50% yield by hydrolysis of **5** (R = H) with concentrated hydrochloric acid. No aldehyde was observed. Small quantities of **12** were also observed together with isoquinaldonitrile during several preparations of **5** (R = H). A solution of 1.00 g. (0.0045 mole) of **5** (R = H) in 10 ml. of ethanol was refluxed for 2 hours and filtered. The ethanol was removed from the filtrate and the residue was dissolved in ether. After washing and drying concentration of the ether gave 0.53 g. (49%) of an oil (ethyl ester of **12**); ir: 1735 cm^{-1}. Treatment of the oil with ethanolic picric acid gave the picrate, m.p. 144-145° (ethanol).

Anal. Calcd. for $C_{21}H_{20}N_4O_9$: C, 53.39; H, 4.27; N, 11.86. Found: C, 53.81; H, 4.32; N, 11.91.

This same oil was obtained during recrystallization of **5** (R = H) from ethanol. Similar treatment of **6** in refluxing ethanol gave 68% of an oil (**13**); ir: 1730 cm^{-1}. Treatment with ethanolic picric acid gave the picrate, m.p. 109-110° (ethanol).

Anal. Calcd. for $C_{22}H_{22}N_4O_9$: C, 54.32; H, 4.56; N, 11.52. Found: C, 54.11; H, 4.57; N, 11.56.

Similar treatment of **11** in refluxing ethanol gave only recovery of **11**.

Reduction of **5** (R = H).

A solution of 2.34 g. (0.01 mole) of **5** (R = H) in 50 ml. of anhydrous tetrahydrofuran was added to a slurry of 0.81 g. of lithium aluminum hydride in 150 ml. of anhydrous tetrahydrofuran and refluxed for 3.5 hours. After cooling, 8 ml. of water was added, the mixture was filtered, and the solvent removed from the filtrate to give 1.8 g. of an oil (**14**); ir: 1615 cm^{-1}; nmr 6.02 (d, 1, J = 7), 5.20 (d, 1, J = 7), 4.30 δ (t, 1). A portion

of this oil was dissolved in methanol and treated with 47% hydrobromic acid to give a hygroscopic solid, m.p. (heating rate dependent) 190-200° (absolute ethanol-absolute ether).

Anal. Calcd. for $C_{13}H_{13}N \cdot HBr \cdot H_2O$: C, 55.33; H, 5.72; N, 4.96; Br, 28.32. Found: C, 55.23; H, 5.52; N, 4.90; Br, 28.32.

A solution of 1.7 g. of the oil (**14**) in 50 ml. of absolute ethanol with 0.09 g. of platinum oxide was hydrogenated at 30 psi. Filtration and evaporation gave 1.33 g. of an oil (**15**) whose crude ir and nmr spectra indicated the absence of the ethylenic groups indicated above for **14**. Treatment of the oil with ethanolic picric acid gave the picrate of 1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine, m.p. 174-175° (ethanol-water) (reported (10), m.p. 173°).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: N, 13.46. Found: N, 13.57.

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