Reissert Compound Studies. XLV.
The Phenanthridine Reissert Compound

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A series of phenanthridine Reissert compounds and Reissert analogs have been prepared using the trimethylsilyl cyanide method. The reactions of the conjugate base and fluoroborate salt have been studied and found, generally, to be similar to those of the isoquinoline Reissert compounds.

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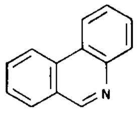
In comparison with the large volume of work [1] that has appeared on the Reissert compounds of quinoline and isoquinoline, relatively little has appeared on the Reissert compounds of phenanthridine (**1**). In 1952 Wittig and coworkers [2] prepared Reissert compounds **2-5** by reaction of phenanthridine with hydrogen cyanide and acid chlorides in anhydrous benzene. They also reported [2] on the acid-catalyzed hydrolysis of these compounds to aldehydes and phenanthridine-6-carboxylic acid. Later [3], Reissert compounds **2, 6** were prepared from phenanthridine using the more convenient methylene chloride-water solvent system. We now report on the investigation of the chemistry of the phenanthridine Reissert compounds.



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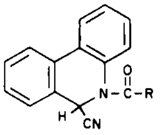
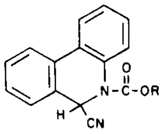
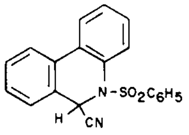


2 R = $-C_6H_5$
3 R = $-CH=CH-C_6H_5$
4 R = $-(-CH=CH-)_2-C_6H_5$
5 R = $-(-CH=CH-)_3-C_6H_5$
6 R = $-C_6H_4-OCH_3-p$
7 R = CH_3
8 R = $-(CH_2)_3-Cl$
9 R = $-C_6H_4CH_2Cl-o$



10 R = C_2H_5
11 R = $CH_2C_6H_5$
13 R = CH_2CH_2Cl



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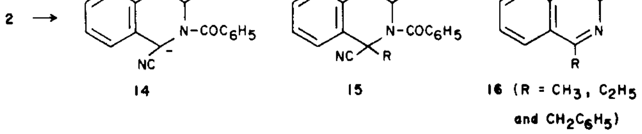
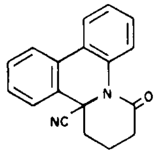


16 (R = CH_3, C_2H_5 and $CH_2C_6H_5$)



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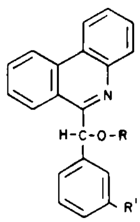
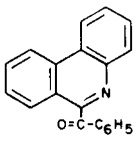


19a R = COC_6H_5 ; R' = OCH_3
19b R = R' = H



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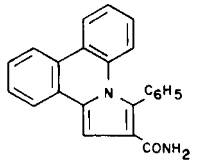

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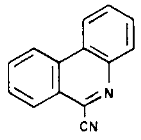

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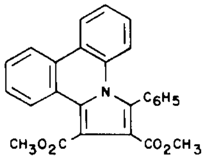

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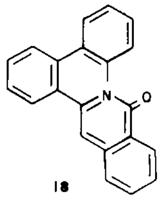

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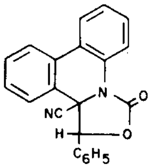

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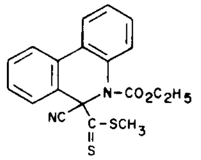

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It was found that the phenanthridine Reissert compound **2** could be obtained from phenanthridine in consistently high yields by the slow addition of freshly distilled benzoyl chloride in methylene chloride to trimethylsilyl cyanide in anhydrous methylene chloride. In a similar manner Reissert compounds **7-9** and Reissert analogs **10-13** were prepared from the appropriate acid chlorides, chloroformates, and benzenesulfonyl chloride respectively. The properties of these compounds are shown in Table I.

The phenanthridine Reissert compound **2** was readily converted to the conjugate-base **14** which on treatment with an alkyl halide gave **15** which was hydrolyzed with aqueous-ethanolic potassium hydroxide to give a series of 6-alkylphenanthridines (**16**; R = CH_3, C_2H_5, $CH_2C_6H_5$). The Reissert compound **8** on similar conversion to its conjugate-base **14** underwent intramolecular alkylation to

Table I

Reissert Compounds and Reissert Analogs

				Analysis %					
				C		H		N	
Compound	Yield, %	Mp, °C	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
2	90	146-147	$C_{21}H_{14}N_2O$	(reported 140-142 [3], 140-145° [6])					
7	81	173-174	$C_{16}H_{12}N_2O$	77.40	77.44	4.87	4.90	—	—
10	72	108-109	$C_{17}H_{14}N_2O_2$	73.36	73.15	5.07	5.03	10.06	10.16
11	56	129-129.5	$C_{22}H_{16}N_2O_2$	77.63	77.62	4.73	4.71	8.22	8.16
12	26	124-124.5	$C_{20}H_{14}N_2SO_2$	69.35	69.24	4.07	4.05	—	—
8	81	95-96	$C_{18}H_{15}N_2OCl$	69.55	69.53	4.86	4.88	—	—
9	65	190-191.5	$C_{22}H_{15}N_2OCl$	73.62	73.48	4.21	4.17	—	—
13	54	124-125	$C_{17}H_{13}ClN_2O_2$	65.27	65.17	4.19	4.11	—	—

give the cyclization product **17**. Similar treatment of **9** gave **18**.

Although the conjugate-base **14** reacted, in the expected fashion, with 3-methoxybenzaldehyde to give the ester **19a**, attempted reaction of **14** with *N*-methyl-4-piperidone resulted only in the isolation of the rearrangement product **20**. Reaction of the anion **10** with benzaldehyde at very low temperature gave **21**, while reaction at room temperature gave **19b**. Michael type addition of **14** and acrylonitrile led to the cyclization product **22**. Reaction of **10** with carbon disulfide and sodium hydride in the presence of methyl iodide gave **23**.

Treatment of the Reissert analog **12** with base gave rise to 6-cyanophenanthridine (**24**).

The phenanthridine Reissert compound **2** reacts with fluoroboric acid in glacial acetic acid to give a Reissert salt whose structure is assigned in analogy to work in the quinoline series [4]. This Reissert salt readily undergoes 1,3-dipolar addition [5] with dimethyl acetylenedicarboxylate to give dimethyl 3-phenylpyrrolo[5,6-*f*]phenanthridine-1,2-dicarboxylate (**25**).

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 710-B spectrophotometer and proton magnetic resonance spectra were measured on a Hitachi Perkin-Elmer R24B spectrophotometer using tetramethylsilane as an internal standard. Microanalysis were determined by Spang Micro-analytical laboratory, Eagle Harbor, Michigan.

5-Benzoyl-6-cyano-5,6-dihydrophenanthridine (**2**).

To a well stirred solution of 1.0 g (0.005 mole) of phenanthridine, 0.69 g (0.007 mole) of trimethylsilylcyanide in 25 ml of anhydrous methylene chloride was added 1.05 g (0.007 mole) of benzoyl chloride in methylene chloride over a period of four hours. The reaction mixture was stirred overnight at room temperature and the solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The methylene chloride solution was dried (sodium sulfate), evaporated and the residue crystallized from 95% ethanol to give 1.4 g (90%) of (**2**), mp 146-147° (Reported 140-142° [3] and 140-145° [6]). The compounds in Table I were prepared by a similar procedure. The ir and pmr spectra were consistent with the assigned structures.

Preparation of 6-Alkylphenanthridines (**16**).

To a stirred solution of 0.5 g (0.0016 mole) of 5-benzoyl-6-cyano-5,6-dihydrophenanthridine (**2**) and an alkyl halide (0.0016 mole) in 15 ml of anhydrous dimethylformamide was added 0.07 g (0.0016 mole) of 50% sodium hydride in oil dispersion. The mixture was stirred under a nitrogen atmosphere for 5 hours and poured into 150 g of ice. The solid obtained was subjected to hydrolysis, without further characterization, by refluxing it with 40% potassium hydroxide in a 1:1 ethanol-water system. The product was isolated by removing ethanol and extracting the aqueous layer with chloroform several times. The combined extract was washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give the product which was recrystallized by appropriate solvent system. R = CH_3 (75% from petroleum ether), mp 83-84° (reported [7] mp 84°); R = C_2H_5 (78% from petroleum ether), mp 55-56° (reported [8] mp 55.5°); R = $CH_2C_6H_5$ (80% from methanol), mp 112-113° (reported [9] mp 112).

Cyclization of 6-Cyano-5-(4-chlorobutyryl)-5,6-dihydrophenanthridine to (**17**).

To a well stirred solution of 0.5 g (0.001 mole) of **12** in 15 ml of anhydrous dimethylformamide at 0-5° under nitrogen atmosphere was added 0.1 g (0.002 mole) of 50% sodium hydride in oil. After stirring for two hours, the mixture was poured onto ice and the product filtered. The product was washed with water and ethanol and recrystallized from ethanol to give 0.20 g (74%) of **17**, mp 158-158.5°, ir (potassium bromide): 2950, 1660, 1600, 1580, 1480, 1420, 1340, 1200 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14. Found: C, 78.69; H, 5.28.

Reaction of **2** With 3-Methoxybenzaldehyde.

To a mixture of 0.5 g (0.001 mole) of **2** and 0.27 g (0.002 mole) of 3-methoxybenzaldehyde in 15 ml of anhydrous dimethylformamide, 0.10 g (0.002 mole) of 50% sodium hydride in oil was added and the mixture was stirred at room temperature for 2 hours under a nitrogen atmosphere, poured into 200 g of crushed ice, and the aqueous layer extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous sodium sulfate and evaporated *in vacuo*. The product obtained was recrystallized from benzene/hexane to give 0.30 g (73%) of ester **19a**, mp 165-166°; ir (potassium bromide): 3050, 2950, 1700, 1580, 1480, 1440, 1250, 1130 cm^{-1}; pmr (deuteriochloroform): δ 8.51-7.10 (m, 17H), 3.71 (s, 3H), 1.55 (s, 1H).

Anal. Calcd. for $C_{28}H_{21}NO_3$: C, 80.16; H, 5.04. Found: C, 80.22; H, 5.12.

Reaction of **2** With *N*-Methyl-4-piperidone.

Using the procedure described above for the reaction of **2** with aldehyde, the product obtained was 6-benzoylphenanthridine (**20**), mp 151-152° (benzene-heptane) (reported [10] mp 152°); ir (potassium bromide): 2950, 1660, 1600, 1590, 1575, 1450, 1375, 1325, 1250 cm^{-1}.

Anal. Calcd. for $C_{19}H_{13}NO$: C, 84.10; H, 4.83. Found: C, 84.17; H, 4.83.

Cyclization of 6-Cyano-5-(2-chloromethylbenzoyl)-5,6-dihydrophenanthridine to (**18**).

To a well stirred solution of 0.5 g (0.0014 mole) of **9** in 10 ml of anhydrous dimethylformamide at −20° under argon atmosphere was added 0.20 g of 50% sodium hydride in oil. After stirring for one hour at −20° and 3 hours at room temperature, the mixture was poured onto ice and the product filtered. The solid was washed with water and cold ethanol and recrystallized from ethanol to give 0.15 g (37%) of **18**, mp 162-163°; ir (potassium bromide): 3050, 2920, 1660, 1615, 1595, 1480, 1335 cm^{-1}.

Anal. Calcd. for $C_{21}H_{13}NO$: C, 85.40; H, 4.43. Found: C, 85.23; H, 4.48.

Reaction of **10** with Carbon Disulfide.

To a solution of 0.30 g (0.001 mole) of **10** and 0.11 g (0.0015 mole) of carbon disulfide in 10 ml of anhydrous dimethylformamide at room temperature was added 0.09 g (0.002 mole) of 50% sodium hydride in oil under an argon atmosphere. The mixture was stirred for 15 minutes and 0.21 g (0.0015 mole) of methyl iodide was added. After stirring at room temperature for 3 hours, the mixture was poured onto 200 g of ice and the product was filtered. The solid was washed with water and cold ethanol and recrystallized from ethanol to give 0.15 g (42%) of **23**, mp 136-137°.

Anal. Calcd. for $C_{19}H_{16}N_2O_2S$: C, 61.93; H, 4.38; N, 7.60. Found: C, 61.87; H, 4.33; N, 7.64.

Reaction of **10** with Benzaldehyde.

a) Room Temperature.

To a mixture of 0.25 g (0.0008 mole) of **10** and 0.14 g (0.0013 mole) of benzaldehyde in 3 ml of anhydrous dimethylformamide was added 0.06 g (0.013 mole) of 50% sodium hydride in oil. The mixture was stirred under a nitrogen atmosphere at room temperature for 3 hours and poured onto ice water. After filtration, the aqueous filtrate was extracted with chloroform and the dried (magnesium sulfate) extract was concentrated *in vacuo* to give a solid. The combined solids were recrystallized from chloroform-petroleum ether to give 0.25 g (80%) of alcohol **19b**, mp 169-171°; ir (potassium bromide): 3250, 3050, 2870, 1600, 1570, 1420 cm^{-1}.

Anal. Calcd. for $C_{20}H_{15}NO$: C, 84.10; H, 5.30; N, 4.91. Found: C, 83.97; H, 5.43; N, 4.78.

b) Low Temperature.

To a solution of 0.25 g (0.0008 mole) of **10** in 3 ml of dry tetrahydrofuran and 6 ml of dry ether was added 0.12 ml (0.0019 mole) of *n*-butyllithium (1.6 *M* solution in hexane) at −78° under an argon atmosphere. After stirring for 15 minutes, 0.14 g (0.0013 mole) of benzaldehyde was added dropwise with stirring at −78°. After stirring in the cold for 1 hour, the mixture was stirred at room temperature for 16 hours. An additional 10 ml of ether was added and the mixture was washed with water, 10% hydrochloric acid, and water. The dried (magnesium sulfate) organic layer was evaporated to give a white solid. Recrystallization from ethanol gave 0.15 g (60%) of **21**, mp 175-176°; ir (potassium bromide): 3050, 1775, 1600, 1500, 1450, 1370 cm^{-1}.

Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.10; H, 4.23; N, 8.25.

Reaction of **2** With Acrylonitrile.

To a well stirred solution of 0.5 g (0.001 mole) of **2** and 0.10 g (0.002 mole) of acrylonitrile in 15 ml of anhydrous dimethylformamide at 0-5° under nitrogen atmosphere was added 0.1 g (0.002 mole) of 50% sodium hydride in oil. After stirring for two hours, the mixture was poured onto ice and the product filtered. The product was washed with water and recrystallized from ethanol to give 0.27 g (81%) of **22**, mp 181-182°; ir (potassium bromide): 1685, 1660, 1630, 1600, 1580, 1480, 1450, 1420, 1380, 1320, 1280 cm^{-1}.

Anal. Calcd. for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.32. Found: C, 81.87; H, 4.69; N, 8.35.

6-Cyanophenanthridine (**24**).

A mixture of 0.15 g (0.0004 mole) of 5-benzenesulfonyl-6-cyano-5,6-dihydrophenanthridine (**8**) and 0.028 g of sodium hydride in 10 ml of xylene was refluxed for 1 hour and cooled. Sodium benzenesulfinate was removed by filtration and the filtrate on concentration gave 0.07 g (91%) of 6-cyanophenanthridine, mp 135-136.5° (reported [11] mp 136-137°).

5-Benzoyl-6-cyano-5,6-dihydrophenanthridine Hydrofluoroborate Salt.

A mixture of 1.10 g (0.0035 mole) of **2** and 5 ml of glacial acetic acid was stirred with warming until solution was complete. The solution was cooled for a while and before any solid could crystallize 5 ml of 50% fluoroboric acid was added with stirring. The solution became orange red, stirring was continued for 30 minutes and the mixture was chilled in an ice-water bath. The product was filtered, washed with ether several times and dried to give 1.37 g of the salt (98%), mp 198-200°; ir (potassium bromide): 3420, 3325, 3200, 1655, 1620, 1545, 1430, 1300, 1245 cm^{-1}; pmr (deuteriochloroform): δ 8.45-7.00 (m, 7H), 2.25-1.90 (m, 8H).

Anal. Calcd. for $C_{21}H_{15}BF_4N_2O$: C, 63.34; H, 3.79; N, 7.03. Found: C, 63.27; H, 3.78; N, 6.94.

Dimethyl-3-phenylpyrrolo[5,6-*f*]phenanthridine-1,2-dicarboxylate (**25**).

A mixture of 0.79 g (0.002 mole) of the fluoroborate salt and 0.42 g (0.003 mole) of dimethyl acetylenedicarboxylate in 25 ml of anhydrous dimethylformamide was heated to 100° slowly and kept at the temperature for 24 hours. The mixture was cooled and poured onto 250 g of crushed ice and stirred well. The precipitated solid was filtered, and dried to give 0.61 g (75%) of pure **25**, mp 136-136.5° (95% ethanol); ir (potassium bromide): 2950, 1710, 1660, 1600, 1530, 1480, 1440, 1405, 1360, 1260 cm^{-1}.

Anal. Calcd. for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.32. Found: C, 81.87; H, 4.69; N, 8.35.

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