Reissert Compound Studies. XLII. Synthesis and Reactions of the 3,4-Dihydro-β-carboline Reissert Compound and Observations on α, β, and γ-Carbolines

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3,4-Dihydro-β-carboline and benzo[*a*]-γ-carboline yielded Reissert compounds. The 3,4-dihydro-β-carboline Reissert compound, through its acid- and base-promoted reactions, was found to be a very useful intermediate in the synthesis of several β-carboline derivatives including tetracyclic compounds. Reaction of the 3,4-dihydro-β-carboline Reissert compound with dichlorodicyanobenzoquinone (DDQ) resulted in the formation of 1-cyano-β-carboline thereby providing the first example of an oxidation of a Reissert compound with DDQ. α-, β- and γ-Carbolines failed to form Reissert compounds under a wide variety of conditions. 7-Azaindole also failed to yield a Reissert compound.

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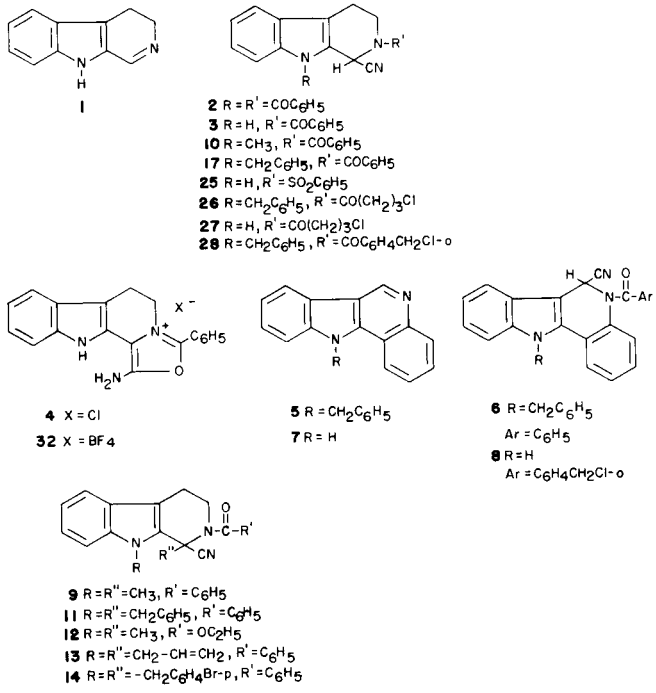
Although the chemistry of the isoquinoline and quinoline Reissert compounds (1,2) has been extensively studied, relatively little was known until recently about the Reissert compound chemistry of other systems. The observation that the phthalazine Reissert compound behaves like the isoquinoline Reissert Compound (3) and affords aza-analogs of isoquinolines has not only added a new dimension to Reissert compound chemistry but has also provided the impetus for the study of other heterocyclic bases. As a result, several heterocyclic systems, in particular the diazaaromatics (4), are receiving increasing attention. We now report on the behavior of α-, β- and γ-carbolines and related compounds towards Reissert compound formation and on the chemistry of the 3,4-dihydro-β-carboline Reissert compound (5) which was investigated in some detail.

The Reissert reaction of 3,4-dihydro-β-carboline (**1**) either by the phase-transfer catalyst method (6) or by the trimethylsilyl cyanide method (7) yielded 1-cyano-2,9-dibenzoyl-1,2,3,4-tetrahydro-β-carboline (**2**), while the use of a catalytic amount of anhydrous aluminum chloride in the trimethylsilyl cyanide procedure afforded 2-benzoyl-1-cyano-1,2,3,4-tetrahydro-β-carboline (**3**) and its hydrochloride salt **4**. It should be noted that similar hydrochloride salts have previously been reported from phthalazine (3) and pyridazine (8). The reaction of 11-benzyl-11*H*-indolo[3,2-*c*]quinoline (**5**) with trimethylsilyl cyanide and benzoyl chloride gave the Reissert compound **6**. 11*H*-Indolo[3,2-*c*]quinoline (**7**) reacted similarly with 2-chloromethylbenzoyl chloride and trimethylsilyl cyanide to give **8**.

The mass spectra of the Reissert compounds **2** and **6** had molecular ions at m/e 405 and 439, corresponding to $C_{26}H_{19}N_3O_2$ and $C_{30}H_{21}N_3O$, respectively. As is the case with other Reissert compounds (1a), the infrared spectrum of **2** lacked the nitrile absorption but showed two carbonyl chromophores (1675 and 1635 cm^{-1}). The peak at 1675 cm^{-1} is attributable to the 9-benzoyl group and that at 1635 cm^{-1} to the 2-benzoyl group.



Reaction of **2** with sodium hydride and excess methyl iodide in anhydrous dimethylformamide gave a compound $C_{21}H_{19}N_3O$ which resulted from methylation at the 1-position and displacement of a benzoyl group by a methyl group. Based on its spectral data (m/e: 329.1536 and ir: 1640 cm^{-1}), the compound was identified as **9**. Confirmation of this structure was had by two unambiguous syntheses, one involving the methylation of the 9-methyl Reissert compound **10** and the other involving the dimethylation of the 9*H*-Reissert compound **3**. The latter reaction was extended to other halides as well; thus, one equivalent of **3** reacted with two equivalents of benzyl bromide and 2.5 equivalents of sodium hydride to afford

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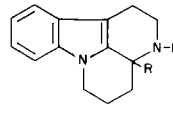
the 1,9-dibenzyl derivative **11**. Compounds **12**, **13**, and **14** were obtained likewise. The use of one equivalent of 1,3-dibromopropane in the place of benzyl bromide in the above procedure led to the tetracyclic compound **15**, which possesses the ring-skeleton of the alkaloid, canthin-6-one (9). A similar reaction of **3** with α,α'-dibromo-*o*-xylene yielded the benzoazepino-β-carboline **16** (10).

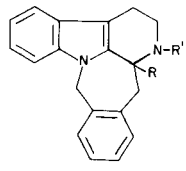
N-Protected-3,4-dihydro-β-carboline Reissert compounds could be used in bis-alkylation reactions. Thus, for example, two equivalents of **17** reacted with one equivalent of α,α'-dibromo-*p*-xylene in the presence of sodium hydride to afford the dimeric 3,4-dihydro-β-carboline derivative **18**.

Alkaline hydrolysis of **9** gave **19**, in sharp contrast to that of a conventional alkylated Reissert compound of the type **20** which gives **21**. The driving force in the conversion of **20** to **21** is the attainment of hetero-ring aromaticity. Such a driving force is absent in **9** (which lacks the 3,4-double bond). This conclusion is further supported by the formation, on hydrolysis, of carboxamides such as **22**, **23** and **24** and also by the observation that the benzenesulfonyl Reissert compound **25** did not yield the expected (11) 1-cyano-3,4-dihydro-β-carboline upon treatment with sodium hydride.

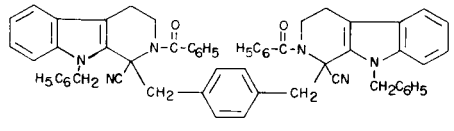
The 4-chlorobutanoyl Reissert compounds **26** and **27** and the 2-chloromethylbenzoyl Reissert compound **28**, when treated with sodium hydride in dimethylformamide, underwent intramolecular alkylation to afford **29**, **30** and **31**, respectively (12-14). The sodium hydride promoted



15 R = CN, R' = COC_6H_5
24 R = $CONH_2$, R' = H



16 R = CN, R' = COC_6H_5
23 R = $CONH_2$, R' = H



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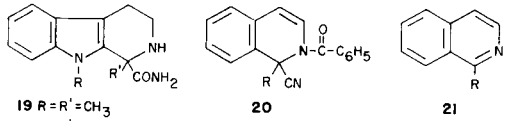
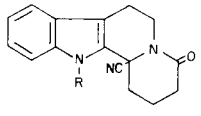


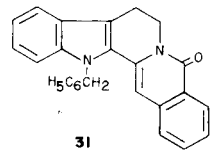
19 R = R' = CH_3
22 R = R' = CH_2-CH_2-CH_2-CH_3

20

21



29 R = $CH_2C_6H_5$
30 R = H



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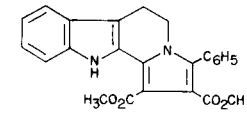

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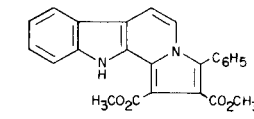

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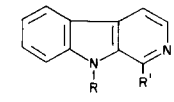
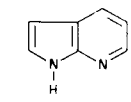


35 R = H, R' = CN
36 R = R' = H
37 R = COC_6H_5, R' = H



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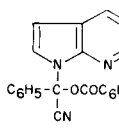

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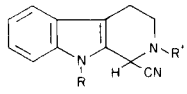
dehydrocyanation accompanying the cyclization of **28** is actually aromatization of the D-ring, a process which is expected to be very facile. Cyclization of **26** and **27** led to the cyano derivatives **29** and **30** (14), respectively, because of the absence of such a driving force.

Treatment of the 3,4-dihydro-β-carboline Reissert compound (**3**) with glacial acetic acid and fluoroboric acid gave the fluoroborate salt **32**, the mechanism for the formation of which is believed to be identical with that for the formation of the Reissert salts of quinoline and isoquinoline. Although at least four different tautomeric forms are possible for the fluoroborate salt of the 3,4-dihydro-β-carboline Reissert compound, the tautomer **32** may reasonably be expected to be the predominant one by analogy with earlier work in the isoquinoline area (15). The hydrochloride salt **4**, which was also the byproduct of the Reissert reaction of 3,4-dihydro-β-carboline, was prepared similarly. Basification of **4** with sodium hydride in dimethylformamide yielded the Reissert compound **3**.

The fluoroborate **32** underwent a 1,3-dipolar addition reaction with dimethyl acetylenedicarboxylate in anhydrous dimethylformamide at 110° to give dimethyl-3-phenyl-5,6-dihydro-11*H*-pyrrolo[1′,2′:1,2]pyrido[3,4-*b*]-indole-1,2-dicarboxylate (**33**) in 39% yield (1). Under similar conditions, the hydrochloride salt **4** gave only 14% of **33**. The hydrochloride **4** appears to be more stable than the fluoroborate **32** and, in fact, it was the only product when **3** was reacted with either ethylcinnamate or vinyl pyridine in dioxane/hydrochloric acid (1). Oxidation of **33** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in the formation of **34**.

The observation that the 5,6-bond in **33** was oxidized by DDQ, prompted the investigation of this reaction with other related substrates. Thus, DDQ reacted with **3** in refluxing benzene to afford 1-cyano-β-carboline (**35**) and the dibenzoate of 2,3-dichloro-5,6-dicyanohydroquinone. Similar reaction of either **9** or **12** was unsuccessful. The conversion of **3** to **35**, which contradicts a recent report (9), probably proceeds through the initial hydride abstraction by DDQ followed by the removal of a proton from another mole of **3** by the phenolate ion formed. The DDQ-assisted

Table I



Compound No.	R	R'	Mp, °C (a)	Yield, %	Formula	Analysis, % Calcd. C	H	N	Found C	H	N
3	H	COPh	229-232 (b)	49	$C_{19}H_{15}N_3O$	75.73	5.02	13.95	75.96	5.16	14.02
2	COPh	COPh	257-260 (b)	31/34	$C_{26}H_{19}N_3O_2$	77.02	4.72	10.37	76.82	4.68	10.35
10	Me	COPh	228-229 (b)	37	$C_{20}H_{17}N_3O$	76.17	5.43	13.33	76.26	5.55	13.23
17	CH_2Ph	COPh	209-210 (b)	39	$C_{26}H_{21}N_3O$	79.77	5.41	10.74	79.85	5.58	10.59
40	H	CO_2Et	163-165 (c)	54	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.61	66.87	5.55	15.65
26	CH_2Ph	$CO(CH_2)_3Cl$	153-154	39	$C_{23}H_{22}ClN_3O$	70.49	5.66	10.73	70.62	5.77	10.58
27	H	$CO(CH_2)_3Cl$	190-192	63	$C_{16}H_{16}ClN_3O$	63.68	5.34	13.93	63.80	5.29	13.84
28	CH_2Ph		190-191 (b)	23	$C_{27}H_{22}ClN_3O$	73.71	5.04	9.55	73.45	5.05	9.48
25	H	SO_2Ph	185-186 (c)	48	$C_{18}H_{15}N_3O_2S$	64.07	4.48	12.46	63.41	4.43	12.35

(a) Recrystallized from ethanol unless otherwise noted. (b) Recrystallized from ethanol-dichloromethane. (c) Recrystallized from heptane-dichloromethane.

Table Ia

Compound	Spectral Data
3	ir (potassium bromide): 3175-2850, 1635, 1615, 1595, 1415, 1305, 1240, 1170, 1050, 910, 760 cm^{-1}; pmr (DMSO-d_6): δ 11.26 (s, 1H), 7.34 (m, 9H), 6.50 (s, 1H), 4.16 (m, 1H), 3.45 (m, 1H), 2.94 (m, 2H).
2	ir (potassium bromide): 3055-2905 (w), 1675, 1635, 1600, 1455, 1410, 1375, 1315, 1220, 1065, 1045, 800 cm^{-1}; ms: m/e 405.1476 ($C_{26}H_{19}N_3O_2$, 12.4%), 300 (1.0%), 273 (3.9%), 272.0938 ($C_{18}H_{12}N_2O$, 17.6%), 247 (2.7%), 246 (28.1%), 168 (1.9%), 140 (1.9%), 106 (4.6%), 105 (100%).
10	ir (potassium bromide): 2935, 1630, 1470, 1430, 1390, 1210, 1060, 1010, 870, 810, 760, 740 cm^{-1}.
17	ir (potassium bromide): 2930, 1640, 1455, 1420, 1385, 1325, 1255, 1190, 1055, 915, 865, 760, 710 cm^{-1}; ms: m/e 391.1683 ($C_{26}H_{21}N_3O$, 100%), 390 (3.4%), 314 (4.1%), 300 (1.9%), 286 (19.3%), 270 (6.0%), 259 (2.4%), 258 (6.3%), 257 (1.4%), 246 (11.2%), 233 (2.6%), 168 (2.2%), 105 (78.3%), 91 (77.3%).
40	ir (potassium bromide): 3300, 3000, 2925, 1700(b), 1480, 1430, 1390, 1310, 1280, 1240, 1190, 1130, 1120, 1030, 910, 765 cm^{-1}.
26	ir (potassium bromide): 2930, 1645, 1465, 1410, 1355, 1315, 1235, 1190, 925, 865, 760 cm^{-1}.
27	ir (potassium bromide): 3350, 2975, 2925, 1640, 1610, 1490, 1470, 1430, 1360, 1310, 1260, 1220, 1050, 1000, 990, 930, 910, 820, 770 cm^{-1}.
28	ir (potassium bromide): 1640, 1460, 1420 cm^{-1}.
25	ir (potassium bromide): 3400, 3055, 2940, 2900, 1580, 1450, 1330, 1305, 1165, 1100, 1115, 950, 910, 865, 770, 755, 705 cm^{-1}.

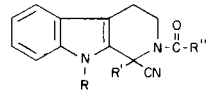
loss of a benzoyl group yields then 1-cyano-β-carboline which undergoes further oxidation to 1-cyano-β-carboline (**35**).

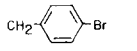
The above reaction when applied to the isoquinoline Reissert compound (**20**, R = H) gave 1-cyanoisoquinoline and the dibenzoate of the hydroquinone. The DDQ method was thus found to provide an alternate route to 1-cyano derivatives from Reissert compounds (1). The potential of 1-cyano-β-carboline in the synthesis of β-carboline alkaloids such as 1-acetyl-β-carboline, 1-carbomethoxy-β-carboline and 1-carbamoyl-β-carboline (16) is obvious. In fact we find that **35** is easily hydrolyzed to the alkaloid, 1-carbamoyl-β-carboline (16).

The success with 3,4-dihydro-β-carboline can be contrasted with the failure of the carbolines themselves to yield Reissert compounds. Elliott (17) reported the dimer of phenylglyoxylonitrile to be the major product of the reaction of β-carboline, potassium cyanide and benzoyl chloride in an aqueous reaction mixture. We now find that β-carboline (**36**) undergoes *N*-benzoylation under a wide variety of Reissert reaction conditions to afford 9-benzoyl-β-carboline (**37**) (18). Several known procedures (1), including the trimethylsilyl cyanide method (7), and a wide variety of experimental conditions were employed but in none of the cases could a β-carboline Reissert compound be obtained. Attempts to form Reissert compounds from *N*-protected-β-carbolines also failed. α- and γ- carbolines behaved like the β-isomer and afforded the corresponding *N*-acyl derivatives.

7-Azaindole (**38**) which may be considered as a two-ring

Table II



Compound No.	R	R′	R″	Mp, °C (a)	Yield, %	Formula	Analysis, % Calcd. C	H	N	Found C	H	N
11	CH_2Ph	CH_2Ph	Ph	176-177	70	$C_{33}H_{27}N_3O$	82.30	5.65	8.73	82.41	5.70	8.77
41	CH_2Ph	Me	Ph	213-214 (b)	60	$C_{27}H_{23}N_3O$	79.97	5.72	10.36	79.81	5.97	10.24
9	Me	Me	Ph	250-251	100	$C_{21}H_{19}N_3O$	76.57	5.81	12.76	76.40	6.14	12.46
12	Me	Me	OEt	147-148 (c)	100	$C_{17}H_{19}N_3O_2$	68.66	6.44	14.13	68.68	6.33	13.94
13	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	Ph	139-140 (b)	77	$C_{25}H_{23}N_3O$	78.71	6.08	11.02	78.62	6.03	11.03
14			Ph	198-199	89	$C_{33}H_{25}Br_2N_3O$	61.99	3.94	6.57	62.25	3.92	6.57

(a) Recrystallized from ethanol-dichloromethane, unless otherwise noted. (b) Recrystallized from ethanol. (c) Recrystallized from heptane-dichloromethane.

Table IIa

Compound	Spectral Data
11	ir (potassium bromide): 3040, 2900, 1645, 1600, 1495, 1455, 1385, 1320, 1250, 1205, 1140, 1055, 1035, 930, 760, 710 cm^{-1}.
41	ir (potassium bromide): 1645, 1455, 1400 cm^{-1}; ms: m/e 405.1828 ($C_{27}H_{23}N_3O$, 42.0%), 390 (1.5%), 379 (1.3%), 378 (5.1%), 350 (4.7%), 349 (4.8%), 314 (1.5%), 302 (1.2%), 300 (3.3%), 288 (2.9%), 284 (23.6%), 273 (4.9%), 272 (1.5%), 271 (1.2%), 259 (1.9%), 244 (4.2%), 233 (9.5%), 232 (1.2%), 183 (2.0%), 105 (100%), 91 (63.4%).
9	ir (potassium bromide): 2930, 2855, 1640, 1475, 1395, 1265, 1245, 1150, 1055, 975, 810, 755 cm^{-1}; ms: m/e 329.1536 ($C_{21}H_{19}N_3O$, 10.4%), 314 (0.8%), 302 (3.3%), 274 (3.7%), 273 (7.1%), 224 (7.6%), 208 (26.3%), 197 (6.4%), 196 (6.5%), 195 (4.9%), 182 (1.9%), 168 (3.8%), 167 (1.4%), 157 (12.6%), 156 (1.4%), 154 (1.6%), 144 (1.5%), 105 (100%).
12	ir (potassium bromide): 2980, 2910, 1685, 1610, 1470, 1405, 1375, 1340, 1320, 1265, 1240, 1210, 1080, 1040, 1025, 900, 785, 765 cm^{-1}; pmr (deuteriochloroform): δ 7.28 (m, 4H), 4.30 (q, J = 7 Hz, 2H), 3.88 (s, 3H), 3.65 (m, 2H), 2.83 (t, J = 6 Hz, 2H), 2.05 (s, 3H), 1.38 (t, J = 7 Hz, 3H).
13	ir (potassium bromide): 3055, 2910, 2855, 1645, 1465, 1445, 1365, 1320, 1245, 1220, 1195, 1180, 1145, 1055, 1005, 950, 930, 810, 760 cm^{-1}.
14	ir (potassium bromide): 3025, 2905, 1640, 1590, 1485, 1465, 1445, 1405, 1365, 1245, 1200, 1080, 1020, 930, 820, 750, 730 cm^{-1}.

analog of α-carboline, reacted with benzoyl chloride and trimethylsilyl cyanide in the presence of a catalytic amount of anhydrous aluminum chloride to yield **39**. This compound, whose structure is supported by spectral data, may be thought of as arising from a 1,2-addition of benzoyl cyanide (formed *in situ*) across the carbon-oxygen double bond of the initially formed 1-benzoyl-7-azaindole. It is of interest to note here that 6-azaindole, under similar conditions, undergoes a Friedel-Crafts acylation to give 3-acyl-6-azaindole (19).

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 spectrometer as potassium bromide pellets. Proton magnetic resonance spectra were determined with a Hitachi Perkin-Elmer R24B spectrometer using tetramethylsilane as an internal standard. Microanalyses were performed by Spang Microanalytical Laboratory and the mass spectrometry results were obtained at the Midwest Center for Mass Spectrometry at the University of Nebraska, supported under the N.S.F. Regional Instrumentation Facilities Program. α- and β-Carbolines, and 7-azaindole were obtained from Aldrich while γ-carboline was prepared according to Buu-Hoi's procedure (20). Indolo[3,2-*c*]quinoline was kindly provided by Hoffman-La Roche, Inc. 3,4-Dihydro-β-carboline was synthesized by the Bischler-Napieralski cyclization of *N*-formyltryptamine (21), which in turn was obtained from tryptamine formate (22). The crude 3,4-dihydro-β-carboline thus prepared was used without further purification.

N-Alkylation of 3,4-dihydro-β-carboline.

A mixture of 1.0 equivalent of 3,4-dihydro-β-carboline, 1.1 equivalents each of 50% sodium hydride and the alkyl halide (benzyl bromide or methyl iodide) was stirred for 2.5 hours in anhydrous dimethylformamide and poured onto ice. The product was filtered, dried and used in Reissert reactions without characterization.

1-Cyano-2,9-dibenzoyl-1,2,3,4-tetrahydro-β-carboline (**2**).
Method A.

To a well-stirred solution of 1.0 g (5.9 mmoles) of 3,4-dihydro-β-carboline (**1**) and 1.75 g (17.6 mmoles) of trimethylsilyl cyanide in 25 ml of dichloromethane was added 2.5 g (17.6 mmoles) of benzoyl chloride. The contents were stirred for 72 hours and the dichloromethane was washed successively with water (2 x 20 ml), 5% hydrochloric acid (2 x 25 ml), water (20 ml), 10% aqueous sodium hydroxide (2 x 25 ml) and water (20 ml). Removal of the solvent from the dried (magnesium sulfate) organic extract, followed by trituration with ethanol afforded 0.74 g. (31%) of **2**. The melting point, analytical data and spectral characteristics of the title compound are included in Table I.

Method B.

To a well-stirred mixture of 2.0 g (11.8 mmoles) of 3,4-dihydro-β-carboline (**1**), 3.05 g (46.9 mmoles) of potassium cyanide and 0.152 g (5% by weight of potassium cyanide used) of benzyltriethylammonium chloride in 30 ml of dichloromethane and 5 ml of water, was added dropwise 6.63 g (47.17 mmoles) of benzoyl chloride over a period of 1 hour. After stirring the contents for an additional 17 hours, the organic layer was separated and worked-up as described in Method A to obtain 1.6 g (34%) of **2**.

2-Benzoyl-1-cyano-1,2,3,4-tetrahydro-β-carboline (**3**).

A mixture of 5.0 g (29.4 mmoles) of 3,4-dihydro-β-carboline (**1**), 0.1 g of anhydrous aluminum chloride, 8.0 g (80.6 mmoles) of trimethylsilyl cyanide and 12.5 g (88.7 mmoles) of benzoyl chloride in 115 ml of anhydrous dichloromethane was stirred for 63 hours. 2-Benzoyl-1-cyano--1,2,3,4-tetrahydro-β-carboline (**3**) which precipitated during this period was filtered, washed with 95% ethanol and dried to give 4.34 g (49%) (see Table I). The filtrate was allowed to stand for 2 days to yield 2.87 g (29%) of **4** (see below).

Preparation of Reissert Compounds in Table I.

A mixture of the appropriate 3,4-dihydro-β-carboline (1 equivalent), trimethylsilyl cyanide (3 equivalents), the appropriate acid chloride (3 equivalents), and a catalytic amount of anhydrous aluminum chloride in anhydrous dichloromethane was stirred for 24-48 hours and worked-up the usual way (with the exception of **25** and **27** which precipitated after a few hours of stirring) to afford the compounds listed in Table I.

2-Benzoyl-1-cyano-1,9-dimethyl-1,2,3,4-tetrahydro-β-carboline (**9**).

To a well-stirred solution of **3** or **2** or**10** (1 equivalent) and methyl iodide (4 equivalents) in anhydrous dimethylformamide at 0-5° under an atmosphere of nitrogen was added 50% sodium hydride (2.5 equivalents) in oil. The contents, after stirring for 2.5 hours, were poured onto ice and the product filtered. The yield, melting point, analytical and spectral data of the title compound are recorded in Table II.

Preparation of Compounds in Table II.

Reaction of 1 equivalent of a Reissert compound and 2 equivalents of the appropriate alkyl bromide, under conditions identical to those described for the preparation of **9**, afforded the compounds listed in Table II.

2-Benzoyl-1-cyano-1-(4-picolyl)-1,2,3,4-tetrahydro-β-carboline.

To 0.63 g (3.84 mmoles) of 4-picolylchloride hydrochloride in 5 ml of anhydrous dimethylformamide was added 0.19 g (3.96 mmoles) of 50% sodium hydride and the mixture stirred well under nitrogen at 5-10°, 0.5 g (1.66 mmoles) of **3** and 0.2 g (4.17 mmoles) of sodium hydride were then added to the mixture, stirred for 2.5 hours and poured onto ice to obtain 0.53 g (81%) of the title compound, mp 226-227° (from ethanol); ir: 3150-3055 (b), 2930, 1660, 1425, 1220, 1180, 1060, 1015, 940, 800, 760 cm^{-1}; ms: m/e 391.1549 ($C_{25}H_{19}N_4O$, M-H]$^+$, 0.43%), 365.1505 ($C_{24}H_{19}N_3O$, M-HCN]$^+$, 17.77%), 364.1426 ($C_{24}H_{18}N_3O$, 8.72%), 336.1487 ($C_{23}H_{18}N_3$, M-HCN-CO]$^+$, 15.75%), 260.1193 ($C_{17}H_{14}N_3$, M-HCN-C_6H_5-CO]$^+$, 11.39%), 198.1151 ($C_{13}H_{14}N_2$, 10.56%), 197.1077 ($C_{13}H_{13}N_2$, 3.39%), 105.0337 (C_7H_5O, 100%), 77.0393 (C_6H_5, 46.04%).

Anal. Calcd. for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28. Found: C, 76.00; H, 5.09; N, 14.31.

3-Benzoyl-3a-cyano-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]-naphthyridine (**15**) and 3-Benzoyl-3a-cyano-1,2,3,3a,4,9-hexahydro[2]benzazepino[2,3,4-*lm*]-β-carboline (**16**).

By a procedure similar to that described for the preparation of **9**, 0.55 g (1.83 mmoles) of **3**, 0.37 g (1.83 mmoles) of 1,3-dibromopropane and 0.22 g (4.58 mmoles) of 50% sodium hydride gave a crude compound which was chromatographed on a column of silica gel and eluted with chloroform. Evaporation of the eluate gave 0.17 g (27%) of **15**, mp 165-167° (from ethanol); ir: 3050, 2950, 1640, 1460, 1410, 1360, 1320, 1250, 1210, 1150, 1050, 1020, 940, 870, 810, 760, 745 cm^{-1}.

Anal. Calcd. for $C_{22}H_{19}N_3O$: C, 77.39; H, 5.61; N, 12.31. Found: C, 77.23; H, 5.66; N, 12.30.

The use of α,α'-dibromo-*o*-xylene in the place of 1,3-dibromopropane in the above procedure gave a 54% yield of **16**, mp 199-200° (from ethanol-dichloromethane); ir: 3050, 2950, 1635, 1575, 1465, 1385, 1340, 1250, 1180, 1140, 1050, 960, 940, 860, 800, 760 cm^{-1}.

Anal. Calcd. for $C_{27}H_{21}N_3O$: C, 80.37; H, 5.25; N, 10.42. Found: C, 80.23; H, 5.25; N, 10.32.

α,α'-Bis[1-(2-benzoyl-9-benzyl-1-cyano-1,2,3,4-tetrahydropyrido[3,4-*b*]indolyl)]-*p*-xylene (**18**).

Following the procedure described for the preparation of **9**, 0.43 g (1.1 mmoles) of **17**, 0.15 g (0.56 mmoles) of α,α'-dibromo-p-xylene and 0.11 g (2.3 mmoles) of 50% sodium hydride yielded 0.34 g (70%) of **18**, mp 304-306° (from ethanol-dichloromethane); ir: 3030, 2920, 1695, 1600, 1510, 1480, 1460, 1425, 1350, 1260, 1185, 1055, 1045, 1015, 755 cm^{-1}.

Anal. Calcd. for $C_{60}H_{48}N_6O_2$: C, 81.42; H, 5.47; N, 9.50. Found: C, 81.14; H, 5.47; N, 9.51.

12b-Cyano-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**30**).

A mixture of 1.5 g (5.0 mmoles) of **27** and 0.48 g (10.0 mmoles) of 50% sodium hydride in 10 ml of anhydrous dimethylformamide was stirred at 5-10° for 2 hours and poured onto ice to yield 0.97 g (73%) of **30**, mp 214-228° (from ethanol-dichloromethane); ir: 3250-3050 (b), 2950, 1630, 1500, 1460, 1440, 1360, 1340, 1300, 1280, 1250, 1165, 1050, 980, 760 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.52; H, 5.70; N, 15.72.

12-Benzyl-12b-cyano-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine (**29**).

The title compound was synthesized from **26** in 62% yield by following the procedure described for the preparation of **30**, mp 197-198° (from ethanol); ir: 3050, 2925, 1645, 1460, 1400, 1310, 1260, 1160, 1050, 970. 900, 860, 755 cm^{-1}.

Anal. Calcd. for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.89; H, 6.07; N, 11.89.

13-Benzyl-5-oxo-5,7,8,13-tetrahydrobenz[*g*]indolo[2,3-*a*]quinolizine (**31**).

A mixture of 0.10 g (0.23 mmoles) of **28** and 0.2 g (4.17 mmoles) of 50% sodium hydride in 3 ml of anhydrous dimethylformamide was stirred at room temperature for 1 hour, poured onto ice, filtered and dried to obtain 0.08 g (92%) of **31**, mp 213-215° (from ethanol); ir: 1640, 1600, 1455, 1355 cm^{-1}; ms: m/e 376.1576 ($C_{26}H_{20}N_2O$, 100%), 375 (8.8%), 374 (1.4%), 299 (3.3%), 285 (41.3%), 284 (11.9%), 283 (3.3%), 91 (30.6%).

Anal. Calcd. for $C_{26}H_{20}N_2O$: C, 82.95; H, 5.36; N, 7.44. Found: C, 82.53; H, 5.70; N, 7.10.

1,9-Dimethyl-1,2,3,4-tetrahydro-β-carboline-1-carboxamide (**19**).

A mixture of 1.02 g (3.1 mmoles) of **9**, 1.0 g (17.8 moles) of potassium hydroxide in 3 ml of water, and 20 ml of ethanol was refluxed for 10 hours (or until a clear solution resulted). Most of the ethanol was then removed *in vacuo*, the contents diluted with water and extracted with chloroform. Evaporation of the dried (magnesium sulfate) chloroform extract gave 0.46 g (61%) of **19**, mp 166-168° (*n*-heptane-dichloromethane); ir: 3380, 3300, 3250-3150, 2975, 2940, 1670, 1560, 1475, 1360, 1220, 1160, 1030, 890, 810, 780, 750 cm^{-1}.

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.15; H, 6.99; N, 17.35.

Preparation of **22**, **23** and **24**.

The same general procedure as described for the preparation of **19** was applicable to **22**, **23** and **24**.

1,9-Di-*n*-butyl-1,2,3,4-tetrahydro-β-carboline-1-carboxamide (**22**).

This compound was obtained in 55% yield, mp 129-130° (from *n*-heptane); ir: 3400, 3250-3150, 2960, 2925, 2860, 1680, 1560, 1480, 1460, 1340, 1190, 1150, 1020, 750 cm^{-1}.

Anal. Calcd. for $C_{20}H_{29}N_3O$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.08; H, 9.02; N, 12.89.

1,2,3,3a,4,9-Hexahydro[2]benzazepino[2,3,4-*lm*]-β-carboline-3a-carboxamide (**23**).

This compound was obtained in 58% yield, mp 234-235° (from ethanol); ir: 3400, 3300, 3150-3100, 2950, 1680, 1580, 1555, 1460, 1350, 1300, 1240, 1120, 1020, 870, 750 cm^{-1}.

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.68; H, 6.03; N, 13.24. Found: C, 75.87; H, 5.91; N, 13.34.

2,3,3a,4,5,6-Hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine-3a-carboxamide (**24**).

This compound was obtained in 25% yield, mp 226-228° (from *n*-heptane-dichloromethane); ir: 3360, 3280, 3200, 2970, 2950, 1675, 1610, 1580, 1445, 1360, 1230, 1030, 880, 760 cm^{-1}.

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.41; H, 6.66; N, 16.36.

1-Amino-3-phenyl-5,6-dihydro-11*H*-oxazolo[3',4':1,2]pyrido[3,4-*b*]indol-4-ium Chloride (**4**).

To a solution of 1.0 g (3.32 mmoles) of **3** in 25 ml of glacial acetic acid was added 25 ml of concentrated hydrochloric acid and the contents allowed to stand for 12 hours with occasional shaking. The red-orange salt that formed during this period was filtered, washed several times with anhydrous ether and dried to obtain 1.03 g (92%) of **4**, mp 213-215° (from ethanol); ir: 3260, 3125 (b), 1685, 1620, 1460, 1350, 1255, 1100, 1060, 990, 965 cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}ClN_3O$: C, 67.55; H, 4.77; N, 12.44. Found: C, 67.58; H, 4.67; N, 12.34.

Basification of **4**.

A mixture of 1.0 g (2.96 mmoles) of **4** and 0.75 g (15.6 mmoles) of 50% sodium hydride was stirred together for 3 minutes in 20 ml of anhydrous dimethylformamide and poured onto ice. Filtration afforded 0.66 g (74%) of **3** identical in all respects with an authentic sample.

1-Amino-3-phenyl-5,6-dihydro-11*H*-oxazolo[3',4':1,2]pyrido[3,4-*b*]indol-4-ium Tetrafluoroborate (**32**).

By following the procedure described for the synthesis of **4**, 1.0 g of (3.32 mmoles) of **3** and 20 ml of fluoroboric acid gave 1.24 g (96%) of **32**, mp 215-218° (from ethanol); ir: 3450, 3375, 1700, 1620, 1570, 1520, 1450, 1290, 1250, 1200, 1100-1080 (b), 1020-1000(b), 770 cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}BF_4N_3O$: C, 58.64; H, 4.14; N, 10.80. Found: C, 58.69; H, 4.15; N, 10.75.

Dimethyl 3-Phenyl-5,6-dihydro-11*H*-pyrrolo[1',2':1,2]pyrido[3,4-*b*]indole-1,2-dicarboxylate (**33**).

A mixture of 1.0 g (2.57 mmoles) of **32** and 0.55 g (3.87 mmoles) of dimethyl acetylenedicarboxylate in 8 ml of anhydrous dimethylformamide was slowly heated to 110° in an oil-bath and kept at that temperature for 19 hours. The contents were then cooled, poured onto ice, the product filtered, dried and chromatographed on a column of silica gel. Elution with chloroform followed by evaporation of the solvent yielded 0.4 g (39%) of **33**, mp 165-167° (from methanol); ir: 3350, 2950, 1690, 1670, 1590, 1480, 1440, 1320, 1280, 1250, 1200, 1170, 1140, 1060, 1020, 785, 765, 745 cm^{-1}; pmr (deuteriochloroform): δ 10.76 (s, 1H), 7.28 (m, 9H), 3.96 (t, J = 7 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.04 (t, J = 7 Hz, 2H).

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 72.06; H, 5.01; N, 7.08.

By following an identical procedure as above, 1.0 g (3.0 mmoles) of **4** gave 0.17 g (14%) of **33**.

Dimethyl 3-Phenyl-11*H*-pyrrolo[1',2':1,2]pyrido[3,4-*b*]indole-1,2-dicarboxylate (**34**).

To 0.47 g (1.17 mmoles) of **33** in 20 ml of dry benzene, was added a solution of 0.275 g (1.2 mmoles) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 10 ml of benzene. The contents were refluxed for 1 hour, cooled and the insoluble filtered. The filtrate was chromatographed on a column of silica gel and eluted with dichloromethane. Evaporation of the eluate afforded 0.30 g. (64%) of **34**, mp 163-164° (from *n*-heptane); ir: 3320, 2960, 1720, 1685, 1640, 1520, 1470, 1460, 1430, 1340, 1260, 1240, 1220, 1140, 1115, 1070, 1020, 960, 750 cm^{-1}; pmr (deuteriochloroform): δ 11.54 (s, 1H), 7.58 (m, 11H), 3.96 (s, 3H), 3.80 (s, 3H).

Anal. Calcd. for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.49; H, 4.56; N, 7.07.

1-Cyanopyrido[3,4-*b*]indole (**35**).

A mixture of 1.0 g (3.32 mmoles) of **3** and 100 ml of dry benzene was refluxed gently for 3 hours (or until a clear solution resulted). To the refluxing solution was added 1.5 g (6.61 mmoles) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 25 ml of benzene over a period of 10 minutes. The contents were refluxed for an additional 45 minutes, cooled and the insoluble material filtered. The filtrate was chromatographed on silica gel and eluted with chloroform to obtain 0.55 g of 2,3-dichloro-5,6-dicyanoquinol dibenzoate, mp 247-248°.

Anal. Calcd. for $C_{22}H_{10}Cl_2N_2O_4$: C, 60.43; H, 2.30; N, 6.41. Found: C, 60.60; H, 2.57; N, 6.32.

Further elution of the column with a 1:1 mixture (by volume) of chloroform and ethyl acetate afforded 0.31 g (48%) of **35**, mp 231-232° (from *n*-heptane-dichloromethane); ir: 3225-2950 (b), 2900-2610 (b), 2250, 1620, 1560, 1500, 1450, 1430, 1325, 1280, 1220, 1070, 850, 750 cm^{-1}; pmr (DMSO-d_6): 12.50 (s, 1H), 8.44 (m, 3H), 7.68 (d, J = 4 Hz, 2H), 7.39 (m, 1H).

Anal. Calcd. for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.51; H, 3.66; N, 21.81.

Isoquinaldonitrile.

Reaction of the isoquinoline Reissert compound (1.0 g) with DDQ (0.87 g) in benzene (15 ml) by the above procedure gave 0.55 g of 2,3-dichloro-5,6-dicyanoquinol dibenzoate and 0.35 g of isoquinaldonitrile, mp 86-87°, reported (11) mp 86-88°.

1-Carbamoyl-β-carboline.

A mixture of 44 mg (0.228 mmoles) of **35** and 0.11 g of potassium hydroxide in 80% ethanol was refluxed for 5.5 hours. The contents were cooled, the solvent removed *in vacuo* and water added. The solid was filtered and dried to get 31 mg (64%) of the title compound, mp 225-226° [reported (16) mp 230°]; ir: 3400, 3160, 1685, 1620, 1425, 1320, 1295, 1265, 1230, 810, 740 cm^{-1}.

5-Benzoyl-11-benzyl-6-cyano-5,6-dihydro-11*H*-indolo[3,2-*c*]quinoline (**6**).

By following the procedure described for the synthesis of **2** (Method A), 0.3 g (0.91 mmoles) of **5**, 0.24 g (2.42 mmoles) of trimethylsilyl cyanide and 0.34 g (2.41 mmoles) of benzoyl chloride gave 0.36 g of **6**, mp 182-184° (from ethanol-dichloromethane); ir: 3050 (w), 1650, 1495, 1360, 1335, 1160, 1130, 1035, 910, 800, 750 cm^{-1}, ms: m/e 439.1684 ($C_{30}H_{21}N_3O$, 1.07%), 348.1124 ($C_{23}H_{14}N_3O$,M-C_7H_7]$^+$, 0.26%), 308.1318 ($c_{22}H_{16}N_2$, M-C_6H_5CO-CN]$^+$, 71.37%), 231.0907 ($C_{16}H_{11}N_2$,M-C_6H_5CO-CN-C_6H_5]$^+$, 1.10%), 217.0767 ($C_{15}H_9N_2$, M-C_6H_5CO-CN-$C_6H_5CH_2$]$^+$, 3.09%), 131.0371 (C_8H_5NO, 9.58%), 105.0339 (C_7H_5O, 16.25%).

Anal. Calcd. for $C_{30}H_{21}N_3O{\cdot}0.4CH_2Cl_2$: C, 77.11; H, 4.64; N, 8.88. Found: C, 77.44; H, 4.51; N, 8.78.

5-(2-Chloromethylbenzoyl)-6-cyano-5,6-dihydro-11*H*-indolo[3,2-*c*]quinoline (**8**).

Following the above procedure 11*H*-indolo[3,2-*c*]quinoline(**7**) and 2-chloromethylbenzoyl chloride gave the title compound in 36% yield, mp 137-138° (from heptane-dichloromethane); ir: 3300 (b), 1645, 1360, 1160, 760 cm^{-1}; ms: m/e: 334.1109 ($C_{23}H_{14}N_2O$, M-HCl-HCN]$^+$, 2.30%), 243.0788 ($C_{16}H_9N_3$, 3.41%), 218.0841 ($C_{15}H_{10}N_2$, 100%), 217.0753 ($C_{15}H_9N_2$, 8.11%), 190.0652 ($C_{14}H_8N$, 11.08%), 153.0105 (C_8H_6C10, 6.37%), 109.0416 (8.71%), 105.0336 (15.64%), 89.0397 (C_7H_5, 9.35%).

Anal. Calcd. for $C_{24}H_{16}ClN_3O{\cdot}CH_2Cl_2$: C, 62.19; H, 3.76; N, 8.70; Cl, 22.03. Found: C, 62.64; H, 3.85; N, 8.75; Cl, 21.28.

Attempted Synthesis of β-Carboline Reissert Compound: Formation of 9-Benzoyl-β-carboline (**37**).

A mixture of 1.0 g (5.95 mmoles) of β-carboline (**36**), 2.38 g (23.99 mmoles) of trimethylsilyl cyanide, a catalytic amount of anhydrous aluminum chloride, and 3.36 g (23.83 mmoles) of benzoyl chloride in 30 ml of anhydrous dichloromethane was stirred for 33 hours at room temperature. The solid that formed during this period was collected by filtration, washed several times with anhydrous benzene and recrystallized from ethanol to obtain 1.4 g (86%) of **37**, mp 132-133°, reported (18) mp 127-128°.

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.45; H, 4.74; N, 10.31.

A 76% yield of 9-benzoyl-β-carboline (**37**) was obtained when the above procedure was repeated in the absence of aluminum chloride.

The same reactants under an atmosphere of nitrogen and in the absence of aluminum chloride gave, after 15 hours of stirring, a 69% yield of **37** (based on unrecovered starting material).

By carrying out the reaction in refluxing chloroform, an 86% yield of **37** was obtained.

The use of a six-fold molar excess of trimethylsilyl cyanide and a prolonged reaction period (13 days) gave an 80% yield of **37**.

The use of phase-transfer catalyst procedure (as described for the preparation of **2** (Method B) gave a 60% yield of 9-benzoyl-β-carboline (**37**).

β-Carboline was recovered (80%) when a mixture of 0.5 g (3.0 mmoles) of **36**, 0.586 g (9.0 mmoles) of potassium cyanide, 2.38 g (9.0 mmoles) of 18-crown-6 and 1.27 g (9.0 mmoles) of benzoyl chloride was stirred for 16 hours in 15 ml of chloroform and worked-up the usual way.

9-(4-Chlorobutanoyl)-β-carboline Hydrochloride.

This compound was obtained in 90% by reacting 0.5 g (3.0 mmoles) of **36**, 0.89 g (9.0 mmoles) of trimethylsilyl cyanide and 1.27 g (9.0 mmoles) of 4-chlorobutyryl chloride in anhydrous dichloromethane for 23 hours, mp 243-245° (from ethanol).

Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O$: C, 58.26; H, 4.56; N, 9.06; Cl, 22.94. Found: C, 58.42; H, 4.45; N, 9.21; Cl, 22.78.

The use of 9-benzyl-β-carboline in the place of β-carboline in the trimethylsilyl cyanide procedure gave a 48% yield of 9-benzyl-β-carboline hydrochloride, mp 269-272° (from ethanol).

Anal. Calcd. for $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; Cl, 12.03; N, 9.50. Found: C, 73.29; H, 5.12; Cl, 12.09; N, 9.55.

Similar use of 9-methyl-β-carboline gave a 74% yield of 9-methyl-β-carboline hydrochloride.

9-Benzyl-β-carboline was recovered in 64% when a mixture of 0.28 g (1.1 mmoles) of 9-benzyl-β-carboline, 0.33 g (3.3 mmoles) of trimethylsilyl cyanide and 0.21 g (2.5 mmoles) of ethyl chloroformate was stirred for 23 hours in 10 ml of anhydrous dichloromethane and worked-up the usual way.

Attempted Synthesis of α-Carboline Reissert Compound: Formation of 9-Benzoyl-α-carboline.

The use of α-carboline in the place of β-carboline in the procedure for the attempted synthesis of β-carboline Reissert compound gave a 71% yield of 9-benzoyl-α-carboline (based on unrecovered starting material), mp 117-118° (from ethanol), reported (23) mp 78-79°.

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.29; H, 4.48; N, 10.20.

α-Carboline was recovered almost quantitatively when a mixture of 0.5 g (3.0 mmoles) of α-carboline, 0.482 g (3.6 mmoles) of silver cyanide and 0.422 g (3.0 mmoles) of benzoyl chloride was stirred for 4 hours and filtered.

Attempted Synthesis of γ-Carboline Reissert Compound: Formation of 5-Benzoyl-γ-carboline.

γ-Carboline (1.0 g, 5.9 mmoles) and 1.46 g (14.8 mmoles) of trimethylsilyl cyanide were stirred together in 20 ml of dichloromethane under an atmosphere of nitrogen. Benzoyl chloride (2.5 g, 17.8 mmoles) was then introduced and the contents stirred for 18 hours. Removal of the solvent afforded 1.84 g (100%) of 5-benzoyl-γ-carboline hydrochloride, mp 219-222° (from chloroform); ir: 3050, 2750-2500 (b), 1700 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}ClN_2O$: C, 70.01; H, 4.20; Cl, 11.48; N, 9.07. Found: C, 69.68; H, 4.17; Cl, 11.42; N, 9.13.

The phase transfer catalyst procedure led to the recovery of γ-carboline in 45% yield.

Attempted Synthesis of 7-Azaindole Reissert Compound: Formation of **39**.

By following the procedure described for the preparation of **3**, 2.0 g (16.93 mmoles) of **38**, 4.20 g (42.33 mmoles) of trimethylsilyl cyanide, 0.1 g of anhydrous aluminum chloride and 6.0 g (42.55 mmoles) of benzoyl chloride gave, after usual work-up, 0.64 g (11%) of **39**, mp 150-152° (from ethanol); ir: 3120 (w), 3050 (w), 1730, 1590, 1420, 1270, 1070, 1030, 920, 760 cm^{-1}; ms: m/e 353.1172 ($C_{22}H_{15}N_3O_2$, 1.24%), 248.0819 ($C_{15}H_{10}N_3O$, M-C_6H_5CO]$^+$, 5.30%), 232.0867 ($C_{15}H_{10}N_3$, M-C_6H_5COO]$^+$, 18.97%), 231.0797 ($C_{15}H_9N_3$, M-C_6H_5COOH]$^+$, 14.02%), 222.0775 ($C_{14}H_{10}N_2O$, M-C_6H_5COCN]$^+$, 5.86%).

Anal. Calcd. for $C_{22}H_{15}N_3O_2$: C, 74.77; H, 4.28; N, 11.89. Found: C, 74.66; H, 4.27; N, 11.92.

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