Reissert Compound Studies. XXXIX. A Novel Approach to the Berbine and 6-Azaberbine Systems and Related Derivatives of Ellipticine

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A new synthetic method for the construction of the berbine, 6-azaberbine, and indoloberbine ring skeletons is reported. Treatment of heterocyclic bases such as isoquinolines, phthalazines, and ellipticine with 2-chloromethylbenzoyl chloride and trimethylsilyl cyanide gave the corresponding Reissert compounds. Treatment of these Reissert compounds with sodium hydride resulted in intramolecular cyclization with loss of hydrogen cyanide.

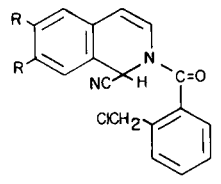
J. Heterocyclic Chem., **18**, 71 (1981).

The application of Reissert compounds (1,2) to the synthesis of isoquinoline alkaloids and related compounds (3) is well known. *N*-(ω-chloroalkanoyl)Reissert compounds are reported to undergo intramolecular alkylation in the presence of sodium hydride to give benzoquinolizines and related compounds (4). We now report on an extension of this chemistry to make available a novel and facile method of synthesis of berbines and azaberbines, and also related compounds derived from ellipticine.

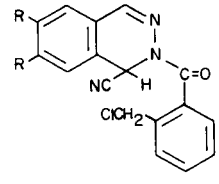
Reaction of isoquinoline, 6,7-dimethoxyisoquinoline, phthalazine, and 6,7-dimethoxyphthalazine with 2-chloromethylbenzoyl chloride and trimethylsilyl cyanide (5) in the presence of a catalytic amount of aluminum chloride gave the Reissert compounds **1-4**. A similar reaction of ellipticine, 6-benzylellipticine, and 9-methoxyellipticine yielded, without the use of aluminum chloride, the Reissert compounds **5-7** (6). Trimethylsilyl cyanide has seen increasing use in recent years as a cyanide source. The trimethylsilyl cyanide method (5) of Reissert compound formation is a convenient one and involves an alternative to the use of potassium cyanide (1,2) as a source of cyanide.

Reaction of Reissert compounds **1** and **2** with sodium hydride in dimethylformamide at 0-5° took place with both intramolecular displacement of the chloride ion by the Reissert anion and with elimination of hydrogen cyanide to give **8** and **9**, respectively. Compound **9** had been synthesized previously by an alternative route and converted into 2,3-dimethoxyberbine (**10**) (7). Thus, the conversion of 6,7-dimethoxyisoquinoline to **9** via the Reissert compound **2** is in fact a synthesis of the berbine **10**. Treatment of **8** with lithium aluminum hydride followed by sodium borohydride as described (7) for the conversion of **9** to **10**, gave berbine (**11**) (9).

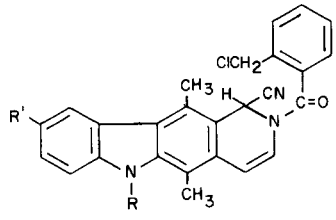
Reaction of the phthalazine Reissert compound **4** with sodium hydride took place in the same manner to give the 6-azaberbine derivative **12**. Similar reaction of **3**, however, led to cyclization that was not accompanied by loss of hydrogen cyanide. The cyanoazaberbine derivative **13** was obtained in this case. The reason for the isolation of **13** in-



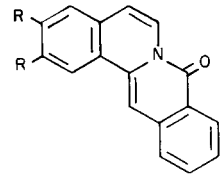
1 R = H
2 R = OCH_3



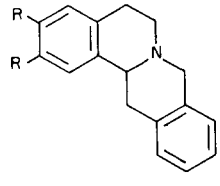
3 R = H
4 R = OCH_3



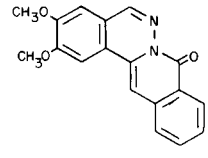
5 R = R' = H
6 R = $C_6H_5CH_2$ –; R' = H
7 R = H; R' = OCH_3



8 R = H
9 R = OCH_3



10 R = OCH_3
11 R = H



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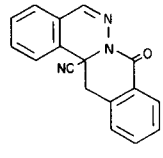
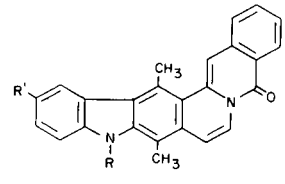


13



14

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stead of the unsaturated analog is not clear. Though compound **13** is relatively stable to both sodium hydroxide and heat, the mass spectrum shows loss of hydrogen cyanide as the major pathway.

Each of the ellipticine Reissert compounds (**5-7**) underwent cyclization and loss of hydrogen cyanide when treated with sodium hydride to give the ellipticine analogs of the type **14**.

The reaction sequences described in this paper make available a highly efficient synthesis of the dehydro-8-oxoberbine system and thus the berbines. The use of starting materials such as phthalazine and ellipticines illustrates the potential (10) of this sequence.

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. Mass spectra were determined at the Midwest Center for Mass Spectrometry and microanalyses by Spang Microanalytical Laboratory.

2-(2-Chloromethylbenzoyl)-1-cyano-1,2-dihydroisoquinoline (**1**).

To a well stirred mixture of 2.0 g. (0.0155 mole) of isoquinoline, 3.85 g. (0.0388 mole) of trimethylsilyl cyanide, and 0.05 g. of aluminum chloride in 50 ml. of anhydrous methylene chloride was added 7.33 g. (0.388 mole) of 2-chloromethylbenzoyl chloride. After stirring for 48 hours, the methylene chloride was removed *in vacuo* and the residue triturated with ethanol to give 3.47 g. (73%) of **1**, m.p. 126-128° (from ethanol); ir (potassium bromide): 1660, 1625, 1350, 1160 cm^{-1}; nmr (deuteriochloroform): δ 7.55-6.95 (m, 8H), 6.59 (s, 1H), 6.25 (d, J = 8 Hz, 1H), 5.86 (d, J = 8 Hz, 1H), and 4.88, 4.41 (dd, J = 12 Hz, 2H).

Anal. Calcd. for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07. Found: C, 69.90; H, 4.14; N, 9.08.

2-(2-Chloromethylbenzoyl)-1-cyano-6,7-dimethoxy-1,2-dihydroisoquinoline (**2**).

Using the procedure described for the preparation of **1**, 1.45 g. (0.0077 mole) of 6,7-dimethoxyisoquinoline gave a 35% yield of **2**, m.p. 176-178° (from ethanol); ir (potassium bromide): 1655 cm^{-1}.

Anal. Calcd. for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65. Found: C, 64.98; H, 4.44.

2-(2-Chloromethylbenzoyl)-1-cyano-1,2-dihydrophthalazine (**3**)

Using the procedure described for the preparation of **1**, 2.0 g. (0.015 mole) of phthalazine gave an 88% yield of **3**, m.p. 149-151° (from *n*-heptane-methylene chloride); ir (potassium bromide): 1660, 1610, 1450, 1360, 1345 cm^{-1}; nmr (deuteriochloroform): δ 7.77-7.13 (m, 9H), 6.73 (s, 1H), and 4.78, 4.48 (dd, J = 12 Hz, 2H).

Anal. Calcd. for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.91; N, 13.57. Found: C, 65.96; H, 3.84; N, 13.64.

2-(2-Chloromethylbenzoyl)-1-cyano-6,7-dimethoxy-1,2-dihydrophthalazine (**4**).

Using the procedure described for the preparation of **1**, 1.7 g. (0.0089 mole) of 6,7-dimethoxyphthalazine gave a 55% yield of **4**, m.p. 161-164° (from ethanol-methylene chloride); ir (potassium bromide): 1665, 1600, 1520, 1365, 1250 cm^{-1}; nmr (deuteriochloroform): δ 7.41-7.19 (m, 5H), 6.83 (s, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 4.72, 4.49 (dd, J = 12 Hz, 2H), 3.98 (s, 3H), and 3.83 (s, 3H).

Anal. Calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36. Found: C, 61.83; H, 4.36; N, 11.33.

2-(2-Chloromethylbenzoyl)-1-cyano-1,2-dihydro-6-benzylellipticine (**6**).

A mixture of 0.5 g. (0.0015 mole) of 6-benzylellipticine, 0.37 g. (0.0037 mole) of trimethylsilyl cyanide, and 0.57 g. (0.003 mole) of 2-chloromethylbenzoyl chloride in 10 ml. of anhydrous methylene chloride was stirred at room temperature for 17 hours. Removal of the methylene chloride *in vacuo* followed by trituration with ethanol gave a solid that was chromatographed on silica gel using chloroform to give an 82% yield of **6**, m.p. 190-192° (from ethanol-methylene chloride); ir (potassium bromide): 1670, 1625, 1450, 1330 cm^{-1}; nmr (deuteriochloroform): δ 8.38-8.07 (m, 1H), 7.63-6.88 (m, 13H), 6.32 (s, 2H), 5.68 (s, 2H), 4.96, 4.48 (dd, J = 12 Hz, 2H), 3.02 (s, 3H), 2.55 (s, 3H).

Anal. Calcd. for $C_{33}H_{26}ClN_3O$: C, 76.81; H, 5.08; N, 8.14. Found: C, 76.89; H, 4.97; N, 8.02.

2-(2-Chloromethylbenzoyl)-1-cyano-9-methoxy-1,2-dihydroellipticine (**7**).

The procedure used to prepare **6** gave a 94% yield of **7**, m.p. 270-279°, ir (potassium bromide): 1660, 1635, 1480, 1350, 1220 cm^{-1}.

Anal. Calcd. for $C_{27}H_{22}ClN_3O_2$: C, 71.12; H, 4.86; N, 9.22. Found: C, 71.12; H, 4.86; N, 9.11.

5,6,13,14-Dehydro-8-oxoberbine (**8**).

To a well stirred solution of 2.3 g. (0.0075 mole) of **1** in 15 ml. of anhydrous dimethylformamide at 0-5° under a nitrogen atmosphere was added 0.45 g. (0.0094 mole) of 50% sodium hydride in oil. After stirring for 2 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 1.62 g. (80%) of **8**, m.p. 151-153°, ir (potassium bromide): 1640, 1600, 1580 cm^{-1}; ms: m/e 245.0833 ($C_{17}H_{11}NO$, 100%), 217 (10.8), 216 (15.4), 215 (3.7), 214 (2.8), 190 (1.9), 189 (4.9).

Anal. Calcd. for $C_{17}H_{11}NO$: C, 83.24; H, 4.52;; N, 5.71. Found: C, 83.34; H, 4.52; N, 5.72.

2,3-Dimethoxy-5,6,13,14-dehydro-8-oxoberbine (**9**) and 2,3-Dimethoxyberbine (**10**).

Using the same procedure as described for the conversion of **1** to **8**, 500 mg. of **2** gave a 70% yield of **9**, m.p. 228-230°, reported (7) m.p. 230-231°; ir (potassium bromide): 1655 cm^{-1}. The conversion of **9** to **10** by reaction with lithium aluminum hydride and then sodium borohydride has been reported (7).

Berbine (**11**).

Reaction of 100 mg. of **8** with lithium aluminum hydride followed by sodium borohydride as described (7) for the conversion of **9** to **10** gave 30 mg. of **11**, m.p. 84-85°, reported (8) m.p. 85°, picrate, m.p. 148-150°, reported (8), m.p. 151°.

6-Aza-2,3-dimethoxy-5,6,13,14-dehydro-8-oxoberbine (**12**).

Using the procedure described for the conversion of **1** to **8**, 0.9 g. (0.0024 mole) of **4** gave a 93% yield of **12**, m.p. 276-278° (from ethanol); ir (potassium bromide): 1660 (sh), 1655, 1600, 1505, 1270 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.59; H, 4.57; N, 9.12.

6-Aza-14-cyano-5,6-dehydro-8-oxoberbine (**13**).

Using the procedure described above for the conversion of **1** to **8**, 1.5 g. (0.0048 mole) of **3** gave an 89% yield of **13**, m.p. 280-282° (from ethanol-methylene chloride); ir (potassium bromide): 1670, 1600, 1455, 1310, 1120 cm^{-1}; ms: m/e 273 (1%), 246.0787 ($C_{16}H_{10}N_2O$) (100%), 218 (15%), 190 (7%).

Anal. Calcd. for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.60; H, 4.03; N, 15.27.

Synthesis of Compounds of the Type **14**.

Using the above procedure for the conversion of **1** to **8**, 0.36 g. (0.0007 mole) of **6** gave a 90% yield of **14** (R = $CH_2C_6H_5$, R' = H), m.p. 274-276° (from ethanol-methylene chloride); ir (potassium bromide): 1640, 1600, 1540 cm^{-1}; ms: m/e 452.1888 (100%), 361 (59.6%).

Anal. Calcd. for $C_{32}H_{24}N_2O$: C, 84.93; H, 5.35; N, 6.19. Found: C, 84.80; H, 5.33; N, 6.21.

In a similar manner **14** (R = H, R′ = OCH_3) was obtained in 90% yield from **7**, m.p. 291-294° (from *n*-butanol); ir (potassium bromide): 3310, 2905, 1640, 1570, 1540, 1225 cm^{-1}.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.52; H, 5.11; N, 7.11.

The crude Reissert compound **5** obtained from ellipticine, 2-chloromethylbenzoyl chloride and trimethylsilyl cyanide was treated with sodium hydride as described above to give **14** (R = R′ = H), m.p. 320-323° (from *n*-butanol); ir (potassium bromide): 3300, 3050, 1640, 1570, 1540 cm^{-1}.

Anal. Calcd. for $C_{25}H_{18}N_2O$: C, 82.85; H, 5.01; N, 7.73. Found: C, 82.64; H, 5.10; N, 7.69.

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