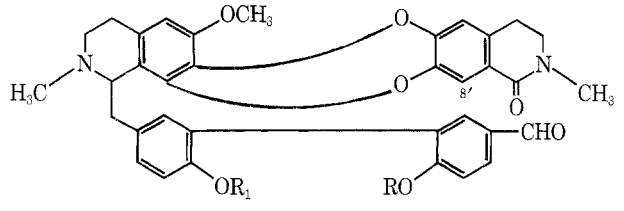
lowed by preparative TLC gave an 8% yield of the desired aldehydo lactam oxidation product **2c**, ν_{max} ($CHCl_3$) 1630 (lactam) and 1705 cm^{-1} (aromatic aldehyde). Close inspection of the NMR spectrum revealed that the C-8′ proton appeared downfield at δ 7.20, consistent with an aromatic hydrogen peri to a lactam carbonyl.[3] Thus, oxidation had taken place, as expected, at the doubly benzylic bond of the isoquinoline unit unsubstituted at C-8′.

The oxidation of tiliacorine acetate (**1d**) was then performed under identical conditions. Basic hydrolysis of the O-acetylated oxidation product **2b** yielded the phenolic aldehydo lactam **2a** whose uv spectrum, λ_{max} (EtOH) 212,



2a, R = H; R_1 = CH_3
b, R = Ac; R_1 = CH_3
c, R = R_1 = CH_3

282, and 310 sh nm (log ϵ 4.10, 3.44 and 2.94), showed a strong bathochromic shift in base to λ_{max} (EtOH–OH^-) 230, 292, and 340 nm (log ϵ 4.00, 3.27, and 3.21). A bathochromic shift of this magnitude is indicative of a phenolic function para to an aromatic aldehyde,[4] so that tiliacorine must be represented by expression **1a**.

It has already been shown that tiliacorine and tiliacorinine are diastereomeric, so that the latter is also represented by **1a**.[5] Nortiliacorinine A and nortiliacorinine B are *N*-nor bases belonging to the tiliacorinine series.[5] Therefore, the present study also settles the position of the phenolic functions of these alkaloids which must be located at C-4″. The absolute configuration of tiliacorine and its analogues still remains to be established.

It should be noted in conclusion that the two lower rings of tiliacorine type alkaloids are linked through a direct carbon to carbon bond, rather than through the much more common diaryl ether bridge.[6] This unusual structural feature precludes facile chemical interrelationship between tiliacorine bases and other bisbenzylisoquinolines of established structure and stereochemistry.[8]

Experimental Section

NMR spectra were obtained on a Varian A-60A with $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were run on an MS-901 spectrometer. All TLC (thin layer chromatography) was on Merck EM F-254 silica gel plates.

General Oxidation Procedure. The bisbenzylisoquinoline, in the present case *O*-methyltiliacorine (**1c**),[2,5] 250 mg, was dissolved in 250 ml of acetone and heated to reflux. Solid $KMnO_4$ (250 mg) was added all at once, and the mixture boiled for an additional 1 h. Filtration of the MnO_2 followed by evaporation of the solvent yielded a gum which was subjected to TLC (10% MeOH–90% $CHCl_3$). Collection of the highest R_f alkaloidal band, detected by short-wave uv light or by the iodoplatinate spray reagent,[7] gave 21 mg (8%) of **2c**, colorless crystals: mp 174–175 °C (MeOH–C_6H_6); λ_{max} (EtOH) 212, 282, and 310 sh nm (log ϵ 4.05, 3.31, and 2.90). The more prominent features of the NMR spectrum were at δ 2.65 (3 H, s, NCH_3), 3.09 (3 H, s, lactam NCH_3), 3.70 (3 H, s, OCH_3), 3.81 (6 H, s, 2 OCH_3), 6.27 (1 H, s, C-5), 7.20 (1 H, s, 8′-H), and 9.80 (1 H, s, -CHO). The mass spectrum showed *m/e* 620 (M^+, $C_{37}H_{36}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), and 255 ($C_{16}H_{15}O_3$); high resolution M^+ calcd 620.2520, found 620.2466.

The oxidation of tiliacorine acetate (**1d**)[5] was carried out under conditions essentially identical with those described above. The yield of aldehydo lactam **2b** was 8%: ν_{max} ($CHCl_3$) 1630 (lactam), 1705 (aromatic aldehyde), and 1765 cm^{-1} (acetate); λ_{max} (EtOH) 212, 270, and 320 sh nm (log ϵ 4.01, 3.44, and 2.86). The mass spectrum showed peaks at *m/e* 648 (M^+, $C_{38}H_{36}N_2O_8$), 605 ($C_{36}H_{33}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), 283 ($C_{17}H_{15}O_4$), and 240 ($C_{15}H_{12}O_3$); high resolution M^+ calcd 648.2770, found 648.2703.

Hydrolysis of 2b. The acetate **2b** (20 mg) was added to 10 ml of a solution of MeOH previously saturated with K_2CO_3. The mixture was stirred at room temperature for 2 h. Work-up provided 18 mg (90%) of **2a**: mp 185–187 °C (MeOH); ν_{max} ($CHCl_3$) 1630 and 1705 cm^{-1}. The NMR spectrum shows peaks at δ 2.35 (3 H, s, NCH_3), 3.08 (3 H, s, lactam NCH_3), 3.80 (9 H, s, 3 OCH_3), 6.28, 6.64, 6.90, 7.17, 7.67, and 7.85 (6 H, each as s, 6 aromatic H), and 9.86 (1 H, s, -CHO). The mass spectrum had peaks at *m/e* 606 (M^+, $C_{36}H_{34}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), and 241 ($C_{15}H_{13}O_3$); high resolution M^+ calcd 606.2364, found 606.2295.

Registry No.—**1a**, 27073-72-9; **1c**, 23944-12-9; **1d**, 58220-09-0; **2a**, 58220-10-3; **2b**, 58220-11-4; **2c**, 58220-12-5.

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(8) **Note Added in Proof.** A similar conclusion regarding the position of the phenolic function in tiliacorine was reached independently by Professor Norman S. Bhacca of Louisiana State University.

Facile Intramolecular Displacement of Fluoride in Reaction of γ-Fluorobutyronitrile with Phenylmagnesium Bromide

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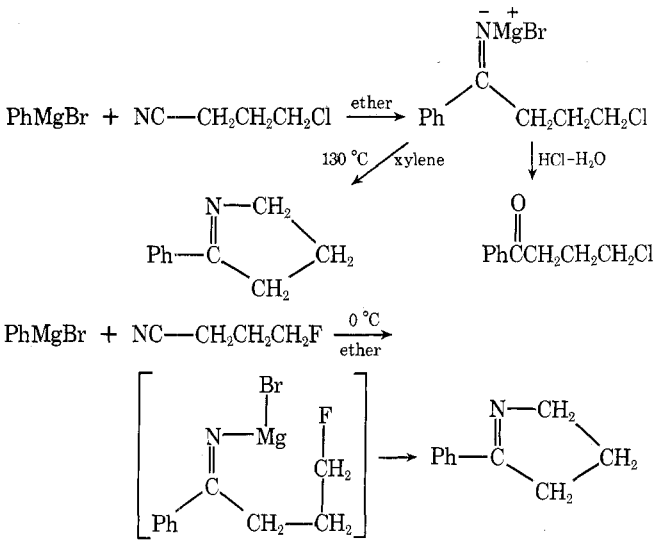
Received November 12, 1975

2-Aryl-1-pyrrolines (5-aryl-3,4-dihydro-2*H*-pyrroles) can be readily synthesized by the addition of aryl Grignard reagents to γ-chloro- or -bromobutyronitrile.[1-4] When cyclization is desired, the magnesium bromide salt of the imine or the free imine is heated. If the ethereal solution of the imine salt is worked up as usual, by acidification and hydrolysis,[5] the γ-halo ketones are obtained in good yields.[1,6] We find that when phenyl Grignard reagent is added to γ-fluorobutyronitrile, the pyrroline is formed even without replacement of solvent and heating.

An ether solution of phenylmagnesium bromide was prepared as usual. Addition of γ-fluoronitrile to this solution produced a more exothermic reaction than normal for aliphatic nitriles. In one run the solution was allowed to reflux during the addition; in another it was kept in an ice bath. The reaction solution was worked up so as to hydrolyze any γ-fluoroimine to the ketone. The only product obtained was identified as 2-phenyl-1-pyrroline.

The very exothermic nature of the Grignard–fluoronitrile reaction and the lack of ketone product suggest that the imine anion readily displaces the fluoride under the mild conditions of the Grignard-to-nitrile addition. Since the chloro- and bromoimine salts do not undergo internal displacement except at high temperature, and since normally Br > Cl ≫ F as leaving groups, we must postulate that the magnesium ion assists the displacement by bonding specifically to the fluorine. The unusual nature of the Grignard reaction is emphasized by the selective displace-



ment of chloride by sodium cyanide from 1-chloro-3-fluoropropane which we used in one preparation of the fluoronitrile.

We have not investigated whether magnesium salts in general easily displace fluoride from alkyl fluorides.

Preparation of 2-Phenyl-1-pyrroline. Phenylmagnesium bromide (0.33 mol) was prepared as usual by slow addition of 53 g of bromobenzene in an equal volume of anhydrous ether to 8 g of magnesium turnings in a round-bottomed flask fitted with a reflux condenser and magnetic stirrer. The solution was then cooled in an ice bath while 21 g (0.24 mol) of γ-fluorobutyronitrile was added dropwise. The addition caused vigorous refluxing of the solution and precipitation of a flaky white substance. After the addition was complete, the entire mixture was poured into a 500-ml beaker half filled with ice and 50 ml of concentrated HCl and was stirred until all solids were dissolved. The cold aqueous layer was washed with ether and placed on a steam bath for 1 h. Extraction of the cooled solution with ether yielded only a trace of an oily substance. Solid sodium carbonate was added to the aqueous solution until it was slightly basic. Warming the solution on a steam bath caused a reddish oil to separate. Extraction with ether yielded 20 ml of a product which was vacuum distilled on a micro-Vigreux column. A slightly cloudy, colorless liquid (13 g) was collected at 102–104 °C (5 Torr). The product was purified by being passed through a small quantity of alumina and then being recrystallized from hexane immersed in dry ice. The resulting clear liquid produced only one peak in VPC analysis: ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 2 H, ortho H), 7.42 (m, 3H, meta and para H), 4.09 (t, J = 8.0 Hz, 2 H, $-CH_2N=$), 2.95 (t, J = 8.0 Hz, 2 H, $CH_2C=N$), 2.00 (quintet, J = 8 Hz, 2 H, $C-CH_2C$); ir (CCl_4) 3030, 2960, 2855, 1610, 1570, 1490, 1440, 1335, 1305, 1035, 1020, 985, 960, 685 cm^{-1}; MS (15 eV) *m/e* (rel intensity) 145 (100), 144 (24), 117 (94), 105, 104, 91, 77, 68.

Anal. Calcd for $C_{10}H_{11}N$: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.83; H, 7.66; N, 9.58.

This procedure was repeated 5 years later by another worker, with identical results. The addition of nitrile to Grignard was done at 0 °C; the acidified solution was not heated.

Preparation of γ-Fluorobutyronitrile. A. Ethylene glycol (250 ml) and 200 ml of toluene were placed in a flask equipped with a Dean-Stark trap, reflux condenser, and drying tube. $KF{\cdot}2H_2O$ (282 g, 3 mol) was added in three portions, with 2–3 h refluxing between additions. In the first 10 h of refluxing, 108 ml of water was removed. Further refluxing overnight removed traces of water. Toluene (150 ml) was then distilled off. To the cooled solution 315 g of 1-bromo-3-chloropropane (Michigan Chemical Co.) was added over 15 min. The mixture was then heated to 100 °C and was stirred vigorously for 8 h. A distillation head was then substituted for the reflux condenser and everything boiling between 70 and 100 °C was collected and dried over calcium chloride. Redistillation yielded 53 g (0.5 mol) of crude 1-chloro-3-fluoropropane (probably containing some of the 3-bromo compound), bp 75–90 °C. This 1-chloro-3-fluoropropane (53 g) was added dropwise to a stirred solution of 50 g of NaCN in 75 ml of Me_2SO. The Me_2SO solution had been preheated to 60 °C and maintained a temperature range of 75–95 °C during addition. The mixture was stirred for 5 h after addition was complete. It was then added to 500 ml of of water and extracted with ether.

The ether layer was washed with 1 N HCl, dried over $CaCl_2$, and distilled. γ-Fluorobutyronitrile (21.5 g, 0.24 mol) was collected as a clear, colorless liquid: bp 162–166 °C; NMR (60 MHz, neat) δ 4.83, 4.05 (2 H, each a t, J = 5 Hz, FCH_2, J_{H-F} = 47 Hz), 2.45 (t, 2 H, J = 6 Hz, CH_2CN), 2.56–1.50 (2 H, complex, roughly a doublet of quintets, middle CH_2, $J_{F-H} \simeq$ 32 Hz); ir (film) 2980, 2910, 2250, 1475, 1430, 1390, 1035, 925, 895 cm^{-1}.

B. $KF{\cdot}2H_2O$ (283 g, 3 mol) was heated under vacuum in a 1-l. flask to drive off most of the water. Glycerine (300 g) was added to the cooled salt. The solution was stirred and warmed to 50 °C, whereupon 126 g of γ-chlorobutyronitrile (Eastman Technical) was added and the pot temperature was gradually increased to 200 °C. A product distilled over between 140 and 160 °C. This distillate was added to 60 ml of chloroform and the organic layer was dried over $MgSO_4$. Distillation provided 42 g (47% yield) of the fluoronitrile, ≥95% pure to VPC analysis.

Registry No.—$KF{\cdot}2H_2O$, 13455-21-5; NaCN, 143-33-9; 2-phenyl-1-pyrroline, 700-91-4; bromobenzene, 108-86-1; γ-fluorobutyronitrile, 407-83-0; 1-bromo-3-chloropropane, 109-70-6; 1-chloro-3-fluoropropane, 462-38-4; γ-chlorobutyronitrile, 628-20-6.

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