chromated, θ-2θ scans). The size of the crystal used for data collection was approximately 0.3 × 0.3 × 0.3 mm. No absorption correction was necessary (μ = 0.902). A total of 1830 independent reflections were measured for θ < 27.8°, of which 1317 were considered to be observed [$I > 2\sigma(I)$]. The structure was solved by direct methods using MULTAN 78[16] and refined by full-matrix least-squares methods. In the final refinement anisotropic thermal parameters were used for the nonhydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.075 and R_w = 0.077 for the 1317 observed reflections. The final difference map had no peaks greater than ±0.6 e Å^{-3}.

Registry No. 2a, 60066-35-5; **2b**, 81767-50-2; **2c**, 71939-83-8; **2d**, 77448-64-7; **2e**, 81724-60-9; **2f**, 80795-28-4; **8**, 80377-52-2.

Supplementary Material Available: Tables I–III listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles for compound **2a** (4 pages). Ordering information is given on any current masthead page.

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Nicotinic Acid Crown Ethers.[1] An Unexpected Facile Etherification Process

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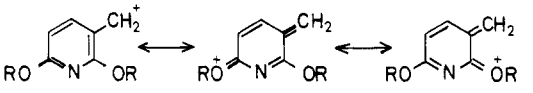
During our studies to functionalize macrocycles containing subheterocyclic rings, the 3-carbinol moiety on a pyridine subunit was of interest. The availability of 2,6-dichloronicotinic acid[2] provided an excellent starting material for (a) generation of the crown ether portion via nucleophilic heteroaromatic substitution and (b) appendage construction via the carboxyl group.

Esterification of the substituted nicotinic acid was accomplished (100%) by Fischer esterification conditions.[3] Although 2-carbethoxypyridine was readily reduced to the carbinol with sodium borohydride,[4] **1** was recovered unchanged under these conditions. However, **2a** was obtained (93%) when **1** was subjected to lithium aluminum hydride–aluminum chloride in ether (Scheme I). Attempted conversion of **2a** directly to **5a** was plagued with competitive side reactions such as the abstraction of the acidic proton by sodium hydride and subsequent intermolecular cyclization(s).

In order to circumvent these rival reactions, **2a** was transformed into the base-stable tetrahydropyranyl ether **3a**. Treatment of **3a** with sodium pentaethylene glycolate or ethoxide under standard conditions[5] gave macrocycle **4a** or **4b**, respectively. The multiplet at δ 4.73 confirmed the presence of the protective group, and, in the case of **4a**, the characteristic α-ϵ-methylenic region supported the presence of the crown ether bridge.

Hydrolysis of **4a** in aqueous ethanol with traces of hydrochloric acid gave the ethyl ether **5b** and *no traces* of the anticipated alcohol **5a**. Use of other aqueous alcoholic solvents resulted in similar results. Only with the exclusion of alcoholic solvents (THF–aqueous HCl) can the desired carbinol **5a** be prepared. For evaluation of the ring substituents, carbinols **2** were quantitatively regenerated by aqueous–alcohol hydrolysis of ethers **3** (X = H or Cl); other acidic conditions[6,7] gave similar results. For elimination of any unusual effects caused by the "crown ether" unit, **4b** was readily transformed to the corresponding ether **6b,c**, and again no traces of the carbinol **6a** were detected. The rationale for this facile etherification process can be envisioned as cleavage of **4** under the acidic conditions to generate a stabilized cation **7**, which is trapped by solvent. Further, treatment of carbinols **5a** or **6a** with acidic alcohol quantitatively gave the corresponding ether.



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An alternate protective procedure was the conversion of **2a** to aldehyde **8** via mild oxidation with acetic anhydride and Me_2SO.[8] Subsequent protection of the formyl group, bridge-formation, and deprotection offered no advantage to generate functionalized subunits.

Experimental Section[9]

2,6-Dichloro-3-(hydroxymethyl)pyridine (2a). To a stirred suspension of $LiAlH_4$ (860 mg) and $AlCl_3$ (3.03 g) in anhydrous ether (100 mL) at 0 °C under nitrogen was added ethyl 2,6-dichloronicotinate (**1**; 5 g, 22.7 mmol). The mixture was refluxed for 3 h, cooled, and quenched with water. The ether layer was separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the crude alcohol, which was chromatographed on a short neutral alumina column eluted with dichloromethane to afford **2a**, as colorless crystals: 3.70 g (93%); mp 62–64 °C; ^{1}H NMR δ 3.30 (s, OH, 1 H), 4.68 (s, py CH_2, 2 H), 7.21 (d, 5-py H, J = 8.2 Hz, 1 H), 7.83 (d, 4-py H, J = 8.2 Hz, 1 H); IR (KBr) 3245, 2910, 1570, 1534, 1420, 1142, 826 cm^{-1}; MS (70 eV) m/e (relative intensity) 178 (M$^+$, 14.8), 142 (100). Anal. Calcd for $C_6H_5Cl_2NO$: C, 40.48; H, 2.83; N, 7.83. Found: C, 40.58; H, 2.67; N, 7.76.

3-[[(Tetrahydropyran-2-yl)oxy]methyl]-2,6-dichloropyridine (3a). To a stirred solution of 3,4-dihydropyran (1 mL) in ether (20 mL) was added **2** (1.6 g, 9.0 mmol) and concentrate HCl (1 drop). After 24 h at 25 °C, potassium hydroxide (3 pellets) was added, and the mixture was stirred and decanted. Concentration, followed by Kugelrohr distillation gave the desired ether **3a**, as a colorless oil: bp 240 °C (1.3 mm); 2 g (85%); ^{1}H NMR δ 1.72 [m, $(CH_2)_3$, 6 H], 3.75 (m, CH_2, 2 H), 4.67 (s, CH, 1 H), 4.79 (s, py CH_2, 2 H), 7.33 (d, 5-py H, J = 8.0 Hz, 1 H), 7.80 (d, 4-py H, J = 8.0 Hz, 1 H); IR (neat) 2940, 1583, 1550, 1440, 1130, 837 cm^{-1}; MS m/e (relative intensity) 261 (M$^+$, 1.3), 160 (100). Anal. Calcd for $C_{11}H_{13}Cl_2NO_2$: C, 50.40; H, 5.34; N, 5.00. Found: C, 50.18; H, 5.30; N, 5.06.

Preparation of Macrocycle 4a. To a suspension of NaH (230 mg) in anhydrous toluene (200 mL) under nitrogen was added slowly pentaethylene glycol (910 mg). The mixture was stirred at 25 °C for 30 min, and then ether **3a** (1 g, 3.8 mmol) in toluene (50 mL) was added. The mixture was heated at 80 °C for 24 h, cooled and quenched with water. The organic layer was separated,

(1) Part 72 of the series: "Chemistry of Heterocyclic Compounds". For previous papers in the "Nicotonic Acid Crown Ethers" series see: (a) Newkome, G. R.; Kawato, T.; Benton, W. H. *J. Org. Chem.* **1980**, *45*, 5423. (b) *Ibid.* **1980**, *45*, 626. (c) Newkome, G. R.; Kohli, D. K.; Kawato, T. *Ibid.* **1980**, *45*, 4508. (d) Newkome, G. R.; Kawato, T. *Ibid.* **1980**, *45*, 629. (e) *Ibid.* **1979**, *44*, 2697. (f) *Ibid.* **1979**, *44*, 2693.

(2) We thank Dr. C. D. Weis of CIBA-GEIGY, Basel, Switzerland, for supplying the sample of 2,6-dichloronicotinic acid.

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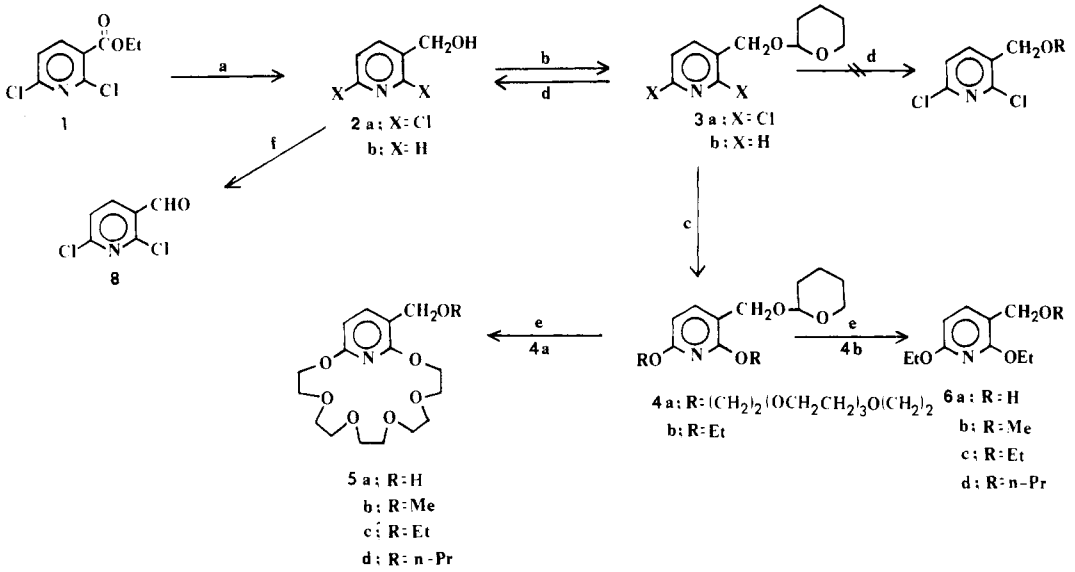
0022-3263/82/1947-2800$01.25/0

Scheme I[a]



[a] (a) $LiAlH_4$, $AlCl_3$, Et_2O; (b) dihydropyran, H^+; (c) NaH, $HOCH_2(CH_2OCH_2)_4CH_2OH$, toluene, 80 °C, 24 h or EtONa, DMF, 90 °C; (d) ROH, HCl; (e) for R = H, THF, H_2O, HCl, 2 h, 25 °C and for R ≠ H, ROH, HCl, 10% H_2, 25 °C, 2 h; (f) Me_2SO, AcOH, Ac_2O, 25 °C, 48 h.

dried over anhydrous sodium sulfate, and concentrated to give the crude macrocycle, which was chromatographed (ThLC) by eluting with cyclohexane/ethyl acetate (1:4) to give the desired 1:1 macrocycle **4a**, as a viscous liquid: 315 mg (19%); ^1H NMR δ 1.55 [m, $(CH_2)_3$, 6 H], 3.56 (s, ε-CH_2, 4 H), 3.61 (m, δ-CH_2, 4 H), 3.71 (m, γ-CH_2, 4 H), 3.88 (m, β-CH_2, THP CH_2, 6 H), 4.60 (m, α-CH_2, py CH_2, 6 H), 4.73 (m, THP CH, 1 H), 6.32 (d, 5-py H, J = 8.0 Hz, 1 H), 7.57 (d, 4-py H, J = 8.0 Hz, 1 H); IR (neat) 2950, 2870, 1605, 1505, 1475, 1310, 1120, 1030 cm^{-1}; MS m/e (relative intensity) 427 (M^+, 3.9), 342 (M^+ - THP, 100). Anal. Calcd for $C_{21}H_{33}NO_8$: C, 59.00; H, 7.78; N, 3.28. Found: C, 58.91; H, 7.80; N, 3.27.

Preparation of 4b was accomplished in a similar manner by the treatment of **3** (2 g) with excess sodium ethoxide in anhydrous DMF at 90 °C. Kugelrohr distillation afforded **4b**, as a colorless oil: 1.55 g (72%); bp 220–230 °C (0.7 mm); ^1H NMR δ 1.36, 1.38 (2 t, CH_3CH_2, J = 7.8 Hz, 6 H), 1.75 [m, $(CH_2)_3$, 6 H], 3.71 (m, CH_2, 2 H), 4.30 4.37 (2 q, CH_3CH_2, J = 7.8 Hz, 4 H), 4.55 (m, py CH_3, 2 H), 6.24 (d, 5-py H, J = 8.4 Hz, 1 H), 7.55 (d, 4-py H, J = 8.4 Hz, 1 H); MS m/e (relative intensity) 281 (M^+, 16), 180 (M^+ - OTHP, 100).

Attempted Hydrolysis of 4. Ether Formation. A solution of aqueous alcohol (50 mL, 10% H_2O), concentrated HCl (1 mL), and **4** (250 mg) was stirred at room temperature for 2 h. A saturated sodium bicarbonate solution was carefully added, and the solution was concentrated in vacuo, extracted with dichloromethane, dried, and concentrated to give an oil, which was chromatographed (ThLC) by eluting with ethyl acetate to afford the ethereal product.

5b from **4a** with methanol: 92%; ^1H NMR δ 3.38 (s, CH_3O, 3 H), 3.55 (s, ε-CH_2, 4 H), 3.60 (m, δ-CH_2, 4 H), 3.70 (m, γ-CH_2, 4 H), 3.88 (t, β-CH_2, 4 H), 4.38 (s, py CH_2, 4 H), 4.55 (m, α-CH_2, 4 H), 6.32 (d, 5-py H, J = 7.8 Hz, 1 H), 7.52 (d, 4-py H, J = 7.8 Hz, 1 H); MS m/e (relative intensity) 357 (M^+, 28.1), 45 (100); IR (neat) 2879, 1590, 1472, 1310, 1113 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.62; N, 3.92. Found: C, 56.72; H, 7.74; N, 3.88.

5c from **4a** with ethanol: 80%; ^1H NMR δ 1.23 (t, OCH_2CH_3, J = 6.8 Hz, 3 H), 3.55 (s, ε-CH_2, 4 H), 3.58 (q, OCH_2CH_3, J = 6.8 Hz, 2 H), 3.60 (m, δ-CH_2, 4 H), 3.71 (m, γ-CH_2, 4 H), 3.88 (t, β-CH_2, 4 H), 4.42 (s, py CH_2, 2 H), 4.56 (m, α-CH_2, 4 H), 6.33 (d, 5-py H, J = 8.5 Hz, 1 H), 7.55 (d, 4-py H, J = 8.5 Hz, 1 H); MS m/e (relative intensity) 371 (M^+, 28.4), 342 [M^+ - (CH_2CH_3), 100]; IR (neat) 2950, 1615, 1600, 1478, 1315, 1125 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_7$: C, 58.21; H, 7.87; N, 3.78. Found: C, 57.96; H, 7.70; N, 3.82.

5d from **4a** with propanol: 80%; ^1H NMR δ 1.93 (t, CH_3, J = 7.3 Hz, 3 H), 1.62 (tq, $CH_2CH_2CH_3$, J = 7.3, 6.8 Hz, 2 H), 3.44 (t, OCH_2CH_2, J = 6.8 Hz, 2 H), 3.55 (s, ε-CH_2, 4 H), 3.62 (m, δ-CH_2, 4 H), 3.70 (m, γ-CH_2, 4 H), 3.88 (t, β-CH_2, 4 H), 4.42 (s, py CH_2, 2 H), 4.55 (m, α-CH_2, 4 H), 6.32 (d, 5-py H, J = 7.8 Hz, 1 H), 7.54 (d, 4-py H, J = 7.8 Hz, 1 H); MS m/e (relative intensity) 385 (M^+, 29.4), 45 (100); IR (neat) 2910, 2860, 1605, 1585, 1470, 1310, 1110 cm^{-1}. Anal. Calcd for $C_{19}H_{31}NO_7$: C, 59.20; H, 8.04; N, 3.63. Found: C, 59.39; H, 8.06; N, 3.42.

6b from **4b** with methanol: 84%; ^1H NMR δ 1.37 (t, $2OCH_2CH_3$, J = 6.8 Hz, 6 H), 3.88 (s, OCH_3, 3 H), 4.30, 4.37 (2 q, OCH_2CH_3, J = 6.8 Hz, 4 H), 4.38 (s, CH_2, 2 H), 6.25 (d, 5-py H, J = 7.8 Hz, 1 H), 7.50 (d, 4-py H, J = 7.8 Hz, 1 H).

6c from **4b** with ethanol: 94%; ^1H NMR δ 1.24 (t, $CH_2OCH_2CH_3$ J = 6.8 Hz, 3 H), 1.37, 1.38 (2 t, $pyOCH_2CH_3$, J = 6.9 Hz, 6 H), 3.55 (q, CH_2OCH_2, J = 6.9 Hz, 2 H), 4.29, 4.34 (2 q, $pyOCH_2$, J = 6.8 Hz, 4 H), 4.42 (s, CH_2O, 2 H), 6.25 (d, 5-py H, J = 7.8 Hz, 1 H), 7.53 (d, 4-py H, J = 7.8 Hz, 1 H); MS m/e (relative intensity) 225 (M^+, 49), 180 (M^+ - OEt, 100).

6d from **4b** with propanol: 98%; ^1H NMR δ 0.93 (t, py CH_3, J = 6.9 Hz, 3 H), 1.36, 1.37 (2 t, OCH_2CH_3, J = 6.9 Hz, 6 H), 1.63 (tq, OCH_2CH_2, 2 H), 3.44 (t, OCH_2(Et), J = 6.9 Hz, 2 H), 4.29, 4.37 (2 q, OCH_2CH_3, J = 6.9 Hz, 4 H), 4.41 (s, py CH_2, 2 H), 6.24 (d, 5-py H, J = 7.8 Hz, 1 H), 7.53 (d, 4-py H, J = 7.8 Hz, 1 H); MS m/e (relative intensity) 2.39 (M^+, 15), 180 (M^+ - OPr, 100).

Hydrolysis of 4. Preparation of Alcohol 5a and 6a. Ether **4** (150 mg) in 75% aqueous THF (20 mL) and concentrated HCl (1 mL) was refluxed for 2 h. The solution was cooled, neutralized with a saturated sodium bicarbonate solution, and concentrated in vacuo to give a residue, which was extracted with dichloromethane. The organic extract was washed with water, dried with anhydrous magnesium sulfate, and evaporated to give a crude oil, which was chromatographed (ThLC) by eluting five times with cyclohexane/ethyl acetate (1:4) to afford the desired alcohol.

Macrocyclic alcohol 5a: 60 mg (50%); ^1H NMR δ 2.00 (s, OH, 1 H), 3.47 (m, ε-CH_2, 4 H), 3.56 (m, δ-CH_2, 4 H), 3.71 (m, γ-CH_2, 4 H), 3.89 (m, β-CH_2, 4 H), 4.56 (s, py CH_2, 2 H), 4.58 (m, α-CH_2, 4 H), 6.32 (d, 5-py H, J = 7.8 Hz, 1 H), 7.47 (d, 4-py H, J = 7.8 Hz, 1 H); IR (neat) 3430, 2870, 1603, 1590, 1473 cm^{-1}; MS m/e (relative intensity) 343 (M^+, 29), 166 (100).

6a: 61%; mp 44–46 °C; ^1H NMR δ 1.38 (t, $2CH_3$, J = 6.9 Hz, 6 H), 2.75 (s, OH, 1 H), 4.29 (q, OCH_2, J = 6.9 Hz, 2 H), 4.39 (q, OCH_2, J = 6.9 Hz, 2 H), 4.54 (s, py CH_2, J = 7.8 Hz, 1 H), 6.22 (d, 5-py H, J = 7.8 Hz, 1 H), 7.44 (d, 4-py H, J = 7.8 Hz, 1 H); MS m/e (relative intensity) 197 (M^+, 65), 140 (100).

2,6-Dichloropyridine-3-carboxaldehyde (8). A mixture of alcohol **2a** (1.12 g, 6.3 mmol) in acetic acid (4 mL) and acetic anhydride (13.2 mL) in Me_2SO (2 mL) was stirred at 25 °C under nitrogen for 2 days. The solution was poured into a cold solution of sodium carbonate (20 g) in water (200 mL) and extracted with

chloroform. The organic extract was washed with water, dried, and concentrated in vacuo to give an oil, which was chromatographed on a silica gel column by eluting with cyclohexane/ethyl acetate (2:1) to give aldehyde **8**: 700 mg (66%); mp 74–74.5 °C; ^{1}H NMR δ 7.40 (d, 4-py H, J = 8.0 Hz, 1 H), 8.15 (d, 5-py H, J = 8.0 Hz, 1 H), 10.36 (s, CHO, 1 H); IR (KBr) 1685 (C=O) cm^{-1}; MS m/e (relative intensity) 176 (M^+, 81), 174 (100). Anal. Calcd for $C_6H_3Cl_2NO$: C, 40.94; H, 1.72; N, 7.96. Found: C, 40.82; H, 1.64; N, 7.85.

Acknowledgment. We thank the National Institutes of Health for partial support of this research.

Registry No. 1, 58584-86-4; 2, 55304-90-0; 3, 81687-96-9; 4a, 81687-97-0; 4b, 81687-98-1; 5a, 81687-99-2; 5b, 81688-00-8; 5c, 81688-01-9; 5d, 81688-02-0; 6a, 81688-03-1; 6b, 81688-04-2; 6c, 81688-05-3; 6d, 81688-06-4; 8, 55304-73-9; 3,4-dihydropyran, 110-87-2; pentaethylene glycol, 4792-15-8.

Synthesis of Cyclohexylidenexanthenes via the Wittig–Horner Reaction

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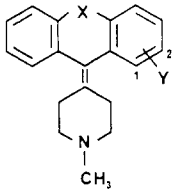
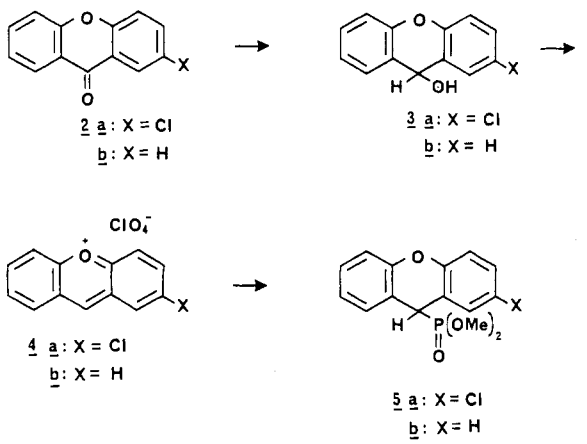
Antihistamine, antiserotonin, neuroleptic, antidepressant, and central depressant properties have been described for a number of *N*-methylpiperidylidene-substituted tricyclic compounds of the general structure **1**.[2]



1 a: X = CH=CH, Y = H
b: X = CH=CH, Y = 2-SCF$_3$
c: X = O, Y = 2-Cl
d: X = O, Y = 1,2 -(CH)$_4$-

Historically, and from a clinical standpoint, the most notable of these is cyproheptadine (**1a**), an effective antipruritic and orexic drug.[3] Several substituted derivatives of **1a**, for example **1b**, are stereoselective neuroleptic agents.[4] Striking neuropharmacologic actions are also produced by piperidylidene derivatives of xanthenes, thioxanthenes, dibenzoxepins, acridans, and related tricycles.[2] The 2-chloro-substituted xanthene clopipazan (**1c**),[5] as well as the 1,2-benzo-fused relative (**1d**),[6] is of particular interest. In both animal and human studies,[7] clopipazan presents a profile suggestive of antipsychotic activity with a minimal potential to produce extrapyramidal side effects.

Scheme I



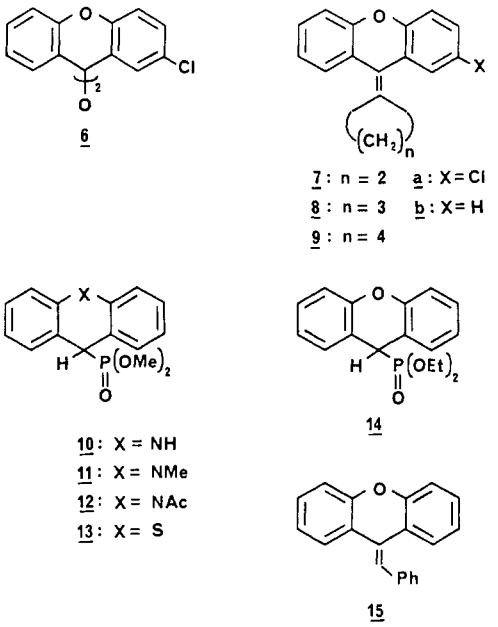
2 a: X = Cl
b: X = H

3 a: X = Cl
b: X = H

4 a: X = Cl
b: X = H

5 a: X = Cl
b: X = H

Chart I



6

7: n = 2 a: X = Cl
8: n = 3 b: X = H
9: n = 4

10: X = NH
11: X = NMe
12: X = NAc
13: X = S

14

15

N-Methylpiperidylidene-substituted tricycles **1** are generally prepared by addition of 1-methyl-4-piperidylmagnesium chloride to the appropriate tricyclic ketone, followed by dehydration of the resulting alcohol.[1] However, this approach was not totally satisfactory for the preparation of **1c**. Problems in forming the necessary Grignard reagent and its cost prompted us to seek other routes. In this paper is described a facile synthesis of clopipazan and other cycloalkylidenexanthenes via the Wittig–Horner reaction. A study of the scope of the reaction is also discussed.

Results and Discussion

Akiba and co-workers[8] described the use of phosphonates **5** derived from **2** (see Scheme I), where the anion of **5**, generated with *n*-butyllithium, is condensed with an aldehyde or ketone. However, this reaction failed with cyclopentanone or cyclohexanone, a result attributed to steric hindrance.[8] We reexamined the condensation of phosphonates **5** with cycloalkanones using different bases and solvents. This reaction proceeds in good yield with six-membered-ring ketones in tetrahydrofuran with either

(1) Present Address: SmithKline Corp., Chemicals Division, 709 Swedeland Road, Swedeland, PA 19479.
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