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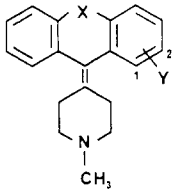
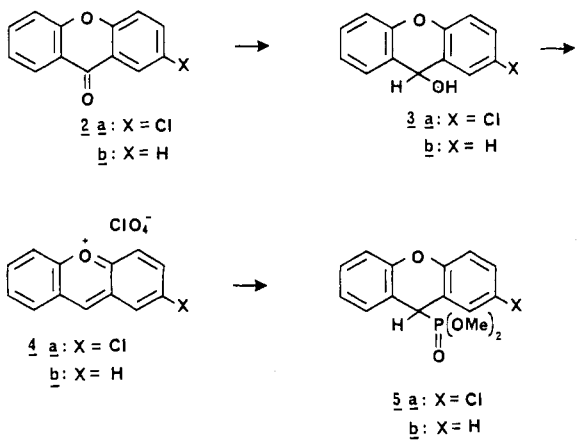
Antihistamine, antiserotonin, neuroleptic, antidepressant, and central depressant properties have been described for a number of *N*-methylpiperidylidene-substituted tricyclic compounds of the general structure **1**.[2]



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



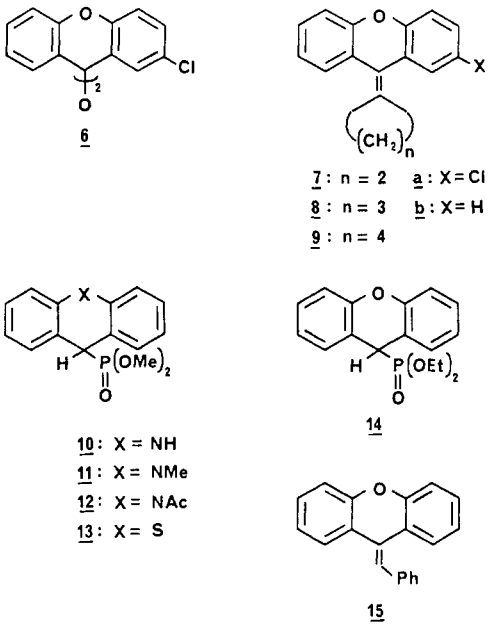
2 a: X = Cl
b: X = H

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

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(2) (a) C. Kaiser, P. J. Fowler, D. H. Tedeschi, B. M. Lester, E. Garvey, C. L. Zirkle, E. A. Nodiff, and A. J. Saggiomo, *J. Med. Chem.*, **17**, 57 (1974). (b) C. Kaiser and P. E. Setler in "Burger's Medicinal Chemistry", 4th ed., M. E. Wolff, Ed., Wiley, New York, 1981, Part III, pp 859–980.
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Table I. Preparation of Cycloalkylidenexanthenes

phosphonate	carbonyl	base	product	yield, % crude/recryst (solvent)	mp, °C	anal.
5a	*N*-methyl-4-piperidone	NaOMe	1c	90 [a]		
5a	*N*-methyl-4-piperidone	NaH	1c	65		
5a	cyclohexanone	NaOMe	8a	92/77 (EtOH)	108-110	C, H, Cl
5a	cyclohexanone	NaH	8a	67		
5b	cyclohexanone	NaOMe	8b	82/56 (Me_2CO)	142-143 [b]	C, H
5b	cyclohexanone	NaH	8b	81/37 [c]		
5b	benzaldehyde	NaOMe	15	83 (EtOH)	113-114.5 (113-113.5) [d]	C, H

[a] Slow-crystallizing oil, identical in all respects with 1c prepared by another route.[5] [b] Reference 16. [c] Isolated after column chromatography. [d] Reference 17.

sodium methoxide or sodium hydride as the base.

Thus, 2-chloroxanthone (**2a**) was reduced with zinc dust in methanol–sodium hydroxide[9] to 2-chloroxanthol (**3a**). The time required for this reaction was dependent on the quality of zinc dust employed. With freshly activated zinc,[10] the reaction was completed in 1 h at room temperature, while with older metal several hours at reflux was required. Other methods of reducing **2a** (aluminum isopropoxide,[11] sodium amalgam,[12,13] sodium borohydride[8]) were unsatisfactory. The xanthol **3a** so produced was unstable to oxidation and probably contained varying amounts of the ether **6**[9] (Chart I). For this reason, **3a** was converted[8] to the perchlorate **4a** without purification. Reaction of the perchlorate with trimethyl phosphite and sodium iodide[8] completed the synthesis of the phosphonate **5a**.

Successful condensation of **5a** with cyclic ketones was base and solvent dependent. *n*-Butyllithium did not provide any of the desired product when **5a** was allowed to react with *N*-methyl-4-piperidone under literature[8] conditions. However, sodium hydride or sodium methoxide in dry tetrahydrofuran provided the condensed product **1c** in good yield. The latter reagent was preferred because it was easier to handle and gave somewhat superior results. Much shorter reaction times were required when 2 equiv of methoxide were used. With six-membered-ring ketones the reaction was very clean, the desired product being the only one observed by TLC. The reaction could be repeated on the unsubstituted xanthenephosphonate **5b** with similar results. In addition to being useful for these cyclic ketones, the reaction also proceeded satisfactorily for a simple aldehyde, e.g., benzaldehyde to give **15** (Table I).

The lack of generality of this reaction was disappointing. Compounds **5** reacted with cyclopentanone or cycloheptanone to give only poor yields of the adducts **7** and **9** as mixtures with xanthone **2**, the principal byproduct. Altering the stoichiometry of reactants or their order of addition or purging the solution with nitrogen had no effect on the result. Since **2** appeared slowly during prolonged reactions, we assume that its formation is the result of the reaction of the anion of **5** with traces of oxygen or some oxygen source in the system, in spite of our attempts to exclude these sources rigorously. The amount of **2** observed may have been increased by interaction with silica or on workup. Phosphonates **10–13** were prepared from acridine and thioxanthene by known procedures, but none of these compounds condensed in the presence of either sodium hydride or sodium methoxide in THF with cyclohexanone. Condensation of diethyl phosphonate **14** with cyclopentanone was also unsuccessful.

The sensitivity of this reaction to what must be a wide variety of poorly understood variables deserves comment. Whereas the preparation of heteroaromatic phosphonates **5** and **10–13** appears general, their propensity to condense with aldehydes and ketones is not. Our success here with bases using sodium as the counterion, in contrast with reported[8] failures with butyllithium (the solvent in both cases was THF), may be ascribed in part to the well-known differences in reactivity of sodium and lithium anions (enolates) in terms of the tightness of the ion pair or state of aggregation,[14] resulting in a higher degree of sensitivity to steric or electronic influences than otherwise might be expected from a naive treatment. The failure of the reaction in methanol suggests that aggregation (solvation) is indeed important. However, while Akiba and co-workers[8] attribute the failure of the condensation with cyclic ketones (and, in fact, butanal) to steric hindrance, they obtain a 95% yield with 4,4′-dichlorobenzophenone, which arguably can be considered more hindered than cycloalkanones. And the sharp decreases in yield as one moves to cycloalkanones other than cyclohexanone suggests that the reaction is quite sensitive to the nature of the electrophile. Evidently, steric hindrance per se is not the only factor to be considered.

In light of the facile condensation of cyclohexanone with phosphonates **5**, its failure to condense with phosphonates **10–13** was unexpected. Here again we observed that subtle changes, this time in the heteroanthracene ring system, are sufficient to influence condensation. The reported successes with **10**, **11**, and **13** are limited to *p*-tolualdehyde, cinnamaldehyde, and 4,4′-dichlorobenzophenone (fails with **13**). Thus, demonstrated generality is lacking in these systems.

Our work suggests that the use of this reaction for the synthesis of ylidene heteroanthracenes must be examined for each case. Clearly, the subtleties of the system are not well understood. Nevertheless, we believe that this sequence offers a synthetically useful alternative for the preparation of certain cycloalkylidenexanthenes, including some medicinally useful compounds.

Experimental Section

All solvents and reagents were purified according to standard procedures.[15] Sodium methoxide was commercial grade (Aldrich).

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Thin-layer chromatography was done on precoated Merck silica gel 60 F-264. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian EM 360 in deuteriochloroform with tetramethylsilane as an internal standard. Mass spectra were obtained by using a Hitachi Perkin-Elmer RMU-6E spectrometer.

2-Chloro-9*H*-10-oxaanthracen-9-ol (3a). Xanthone **2a** (10 g, 43.4 mmol) was suspended in 100 mL of methanol that had been saturated with sodium hydroxide at room temperature. Then freshly activated zinc dust[10] (10 g) was added in a single portion. An intense blue color was generated almost immediately. The reaction was checked for starting material once the blue color had disappeared (TLC, CH_2Cl_2) and was normally complete in 2–4 h. The reaction was then concentrated, the residue suspended in methylene chloride and filtered through Celite, and the filter cake washed thoroughly with methylene chloride. The filtrate was washed with water (twice) and brine, dried ($MgSO_4$), and concentrated to provide 9.53 g (94.4%) of crude white solid that was used directly in the next step.

2-Chloro-10-oxoniaanthracene Perchlorate (4a). Crude xanthol **3a** (5.50 g, 21.5 mmol) was treated[8] in 150 mL of diethyl ether at −78 °C with 15 mL of 70% perchloric acid to provide 5.53 g (77.3% from **2a**) of a gold solid. The melting point of this material, even of the same sample, varied over a 20 °C range. DSC analysis indicated that decomposition which occurred before melting was responsible for the variation in melting point.

2-Chloro-10-(dimethoxyphosphinyl)-9,10-dihydro-9-oxaanthracene (5a). Perchlorate **4a** (5.30 g, 16.8 mmol) was treated[8] in 70 mL of acetonitrile with 3.16 g (25.5 mmol) of trimethyl phosphite at room temperature which gave 5.34 g (97.9%) of crude **5a** as a yellowish solid. Recrystallization from methanol gave 3.85 g (70.6%) of white crystals: mp 144.5–146.5 °C; NMR δ 3.55 (d, J_{P-H} = 11 Hz, 3 H), 3.59 (d, J_{P-H} = 11 Hz, 3 H), 4.42 (d, J_{P-H} = 24 Hz, 1 H), 7.22 (m, 7 H); mass spectrum (FD, chloroform solution), m/e 324 (M^+). Anal. Calcd for $C_{15}H_{14}ClO_4P$: C, 55.49; H, 4.35; Cl, 10.92. Found: C, 55.61; H, 4.40; Cl, 10.88.

Condensation of Phosphonates 5 with Aldehydes and Ketones. General Procedure. The phosphonate **5** and the carbonyl compound (1.1 equiv) were dissolved in dry tetrahydrofuran (1 g of carbonyl/10 mL) under a nitrogen atmosphere, and 2.0 equiv of sodium methoxide or 1.1 equiv of sodium hydride (50% dispersion in mineral oil) was added in a single portion. The reactions were monitored for disappearance of starting material by TLC (CH_2Cl_2) and were complete in 2–4 h at room temperature. The reaction mixture was then concentrated, and the residue was dissolved in methylene chloride, washed with water and brine, dried ($MgSO_4$), and concentrated to give the crude product. Recrystallization was normally achieved from an alcoholic solvent.

Acknowledgment. We thank Richard Warren, Gerald Roberts, and Walter Johnson for mass spectra, Gail Johnson and Edith Reich for microanalyses, and Joseph Buckley for DSC analyses. We extend special thanks to Dr. Carl Kaiser for his help in preparing this manuscript.

Registry No. 1c, 60085-78-1; **2a**, 13210-15-6; **3a**, 13209-86-4; **4a**, 81642-92-4; **5a**, 81642-93-5; **5b**, 14110-88-4; **7a**, 81642-94-6; **7b**, 27426-44-4; **8a**, 81642-95-7; **8b**, 27426-40-0; **9a**, 81642-96-8; **9b**, 81642-97-9; **10**, 65674-21-7; **11**, 65674-22-8; **12**, 81642-98-0; **13**, 39730-71-7; **14**, 81642-99-1; **15**, 27980-52-5; cyclopentanone, 120-92-3; cycloheptanone, 502-42-1; *N*-methyl-4-piperidone, 1445-73-4; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7.

Supplementary Material Available: Table containing melting point, analytical, and ^1H NMR and mass spectral data for **5a**, **8a**,**b**, and **15** (1 page). Ordering information is given on any current masthead page.

Preparation and Electrophilic Trapping of 7-Lithiated Benzoxazoles Generated via Benzyne Cyclization[1]

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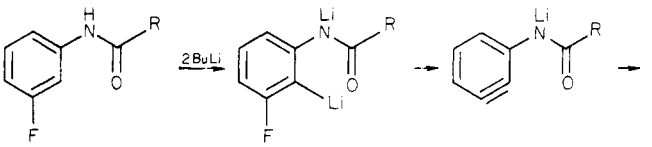
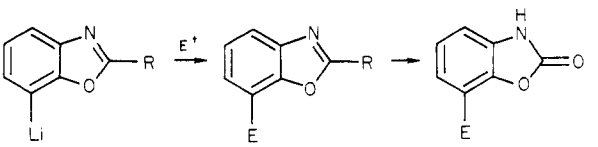
The intramolecular trapping of a benzyne by a side-chain nucleophile to generate a bicyclic system (benzyne cyclization) is a useful synthetic method.[2] Introduced independently by Huisgen[3] and Bunnett,[4] this sequence has been applied to the synthesis of a number of natural products and to a variety of heterocyclic and homocyclic ring systems.[2] One aspect of the benzyne cyclization, which has apparently not been investigated, is the electrophilic trapping of the anion which is generated by the nucleophilic addition to the benzyne. One intramolecular example of such a trapping has been reported.[5] We now report that in the case of benzoxazole formation, the anion so generated can be trapped with representative electrophiles. This additional feature of the benzyne cyclization has obvious implications for the synthesis of a number of 1,2,3-trisubstituted benzenes and substituted bicyclic systems.

Scheme I



1, R = *t*-Bu
2, R = O-*t*-Bu
3, R = C_6H_5



4, R = *t*-Bu
5, R = O-*t*-Bu
6, R = C_6H_5

7-10[a] **11-14**[b]

[a] For **7**: R = *t*-Bu; E = CH_2CH_3; electrophile = CH_3CH_2I; 89% yield. For **8**: R = *t*-Bu; E = SCH_3; electrophile = $(CH_3S)_2$); 56% yield. For **9**: R = *t*-Bu; E = $CH(OH)(4\text{-}ClC_6H_4)$; electrophile = $4\text{-}ClC_6H_4CHO$; 68% yield. For **10**: R = *t*-Bu; E = $4\text{-}t\text{-}BuC_6H_9OH$; electrophile = $4\text{-}t\text{-}BuC_6H_9O$; 70% yield. [b] For **11**: E = CH_3; electrophile = CH_3I; 85% yield. For **12**: E = $CH(OH)C_6H_5$; electrophile = C_6H_5CHO; 52% yield. For **13**: E = $CONH(4\text{-}ClC_6H_4)$; electrophile = $4\text{-}ClC_6H_4NCO$; 56% yield. For **14**: E = SC_6H_5; electrophile = $(C_6H_5S)_2$; 50% yield.

(1) Contribution No. 622 from the Syntex Institute of Organic Chemistry.

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