Reactions of Trivalent Phosphorus Derivatives with Sterically Hindered 4-Bromocyclohexadienones[1]

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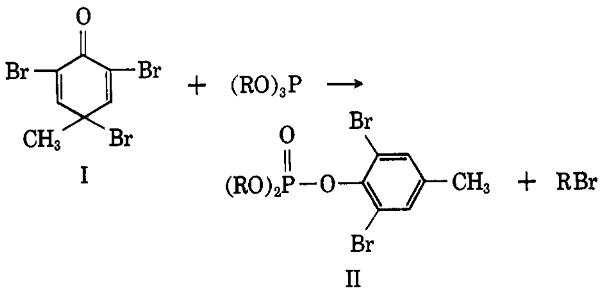
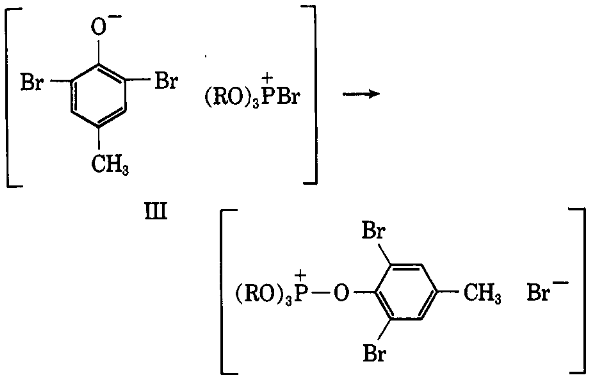
The presence of *t*-butyl groups adjacent to the carbonyl groups of 4-bromocyclohexadienones does not appreciably retard their reactions with trialkyl phosphites. Reaction of trimethyl phosphite with a 4-bromocyclohexadienone having a single *t*-butyl group next to the carbonyl gives the normal phosphate, but reactions of phosphites with 2,6-di-*t*-butyl-4-bromo-4-methylcyclohexadienone (VI) give ethers instead of phosphates. Allyl and butenyl phosphites react with VI to give mixtures of ethers, 4-allyl-(or butenyl-) cyclohexadienones, and *o*-allyl-(or butenyl-) phenols, which arise from *o*-cyclohexadienones. Reaction of trimethyl phosphite with 2,6-di-*t*-butyl-4-bromocyclohexadienone gives a mixture of ethers which is shown to arise from attack of phosphite at the bromine atom. Reaction of triphenyl phosphite with VI, followed by methanolysis, gives 2,6-di-*t*-butyl-4-methylphenyl diphenyl phosphate (XXV).

Reactions of 4-bromocyclohexadienones (I) with trialkyl phosphites have been shown to give excellent yields of dialkyl aryl phosphates (II).[2,3] This reaction was considered to proceed by nucleophilic attack of the phosphite upon the "positive" bromine atom, to give a bromophosphonium-phenoxide ion pair (III), which then collapsed to a trialkoxyaryloxy phosphonium bromide (IV) which, in turn, gave the observed dialkyl aryl phosphate. Although the evidence for this mechanism appeared strong, an alternative reaction path, involving direct attack of the phosphite upon the carbonyl oxygen to give IV in one step, could not be completely discounted.



I

II

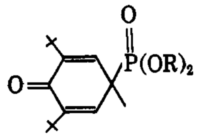


III

IV

To provide further evidence on this point, the reactions of phosphites with 4-bromocyclohexadienones which have *t*-butyl groups in positions adjacent to the carbonyl group have been examined. If direct attack at a carbonyl oxygen occurs in these reactions, the presence of the bulky *t*-butyl groups should markedly decrease the rates of the reactions, and perhaps prevent them completely. Attack at bromine atoms in the 4-positions, however, should be relatively unaffected by the presence of *t*-butyl groups.

A particularly intriguing possibility, if the reaction does occur at the bromine atom, is attack of the bromophosphonium ion, not at the very highly hindered oxygen of the phenolate anion, but at the relatively unhindered *para* position, to give phosphonates such as V. Alternatively, the bromophosphonium ion could act as an alkylating agent rather than a phosphorylating agent. In that case, attack at the oxygen atom or the carbon atoms of the phenoxide ion, giving ethers or cyclohexadienones, respectively, could occur. In practice, most of these types of reactions have been found to occur, the exact nature of the reactions depending on the structure of the phosphite and the ketone.



V

Reactions with Trialkyl Phosphites.—The rates of reactions of 4-bromocyclohexadienones with trialkyl phosphites are not markedly affected by the presence of *t*-butyl groups α to the carbonyl group. Substitution of a *t*-butyl group for one of the α-bromines of I did not cause a noticeable change in the rate of reaction of the ketone with phosphites. The reaction was still essentially instantaneous in benzene solution at room temperature. Replacement of both α-bromine atoms by *t*-butyl groups to give ketone VI did slow the reaction somewhat, but the reaction was nonetheless complete in a few minutes at 0° in benzene, ether, or methylene chloride solutions.

This relatively small change in rate can be readily accounted for by the expected effects of substituents on the stabilities of the phenoxide ions formed by attack of phosphites on the allylic bromine atoms. Very much greater steric inhibition of the reaction rates would have been expected if attack at the carbonyl group were involved in the reaction.

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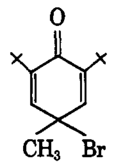
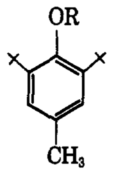
[1] (a) Reactions of Cyclohexadienones, IX. Part VIII: B. Miller, *Tetrahedron Letters*, in press. (b) A short report of part of this work has appeared: B. Miller, *Tetrahedron Letters*, **No. 47**, 3527 (1964).

[2] B. Miller, *J. Org. Chem.*, **26**, 4781 (1961).

[3] B. Miller, *ibid.*, **28**, 345 (1963).

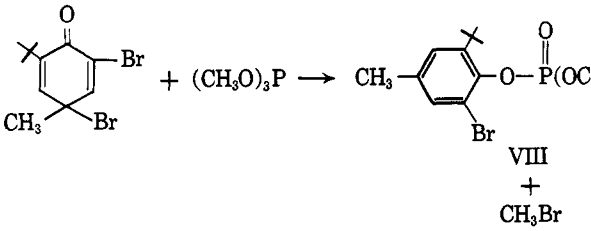


VI



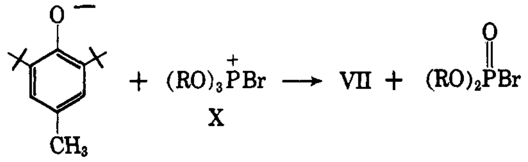
VII

Reaction of trimethyl phosphite with 2,4-dibromo-6-*t*-butyl-4-methylcyclohexadienone gave a 61% yield of the phosphate VIII. Reaction of trimethyl phosphite with the di-*t*-butyl ketone VI, on the other hand,



VIII

gave an 80% yield of the methyl ether VII (R = CH_3), together with some 2,6-di-*t*-butyl-*p*-cresol (VII, R = H). The ether clearly arises from attack of the phenoxide ion IX upon an alkyl group of the bromophosphonium ion X. Dimethyl phosphorobromidate is the other product of the reaction, as is shown by



IX

X

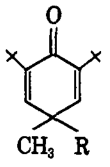
treating the crude reaction mixture with aniline to give a good yield of O,O-dimethylphosphoranilide.

Triethyl and triisopropyl phosphites gave the corresponding ethers VII (R = C_2H_5) and VII (R = *i*-C_3H_7) in yields of 70 and 20%, respectively. The phenol (VII, R = H) accounted for that part of the original dienone which was not converted to the ether. It would be expected that as the degree of substitution on the alkyl groups of the bromophosphonium ion X increases, the amount of elimination occurring in competition with substitution should increase. Indeed, it is rather surprising that as much as a 20% yield of the very highly hindered isopropyl ether should be obtained.

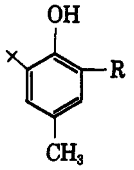
The source of the 20% yield of phenol obtained from reaction between VI and trimethyl phosphite is not apparent. It is possible that traces of moisture remained in VI, even after several recrystallizations from hexane, since the thermal sensitivity of VI precluded any rigorous drying procedure. It seems unlikely, however, that sufficient water remained to account for all the phenol produced. The possibility that the phenoxide ion IX abstracts a proton from a methyl group of X is an interesting one but can hardly be supported at the present time.

The formation of ethers and phosphorobromidates from reaction of VI with phosphites seems to provide conclusive evidence that these reactions proceed by initial attack at bromine rather than at oxygen.

Reaction of VI with Allyl and Butenyl Phosphites.—The reactions of VI with phosphites of allylic alcohols were far more complex than its reactions with phosphites of saturated alcohols. Reaction of VI with triallyl phosphite gave, in addition to an 18% yield of the expected ether VII (R = $CH_2CH{=}CH_2$) and a 25% yield of phenol VII (R = H), a 19% yield of the 4-allylcyclohexadienone XI (R = $CH_2CH{=}CH_2$) and a 38% yield of the *o*-allylphenol XII (R = $CH_2CH{=}CH_2$).

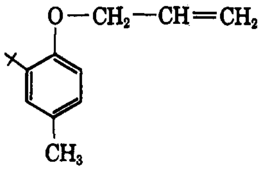


XI

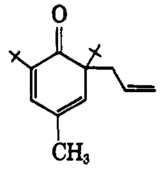


XII

The structure of XII was clearly indicated by its n.m.r. spectrum which showed two hydrogen atoms as doublets ($J \cong 1$ c.p.s.) at (τ-values) 3.16 and 3.36 (aromatic protons in a *meta* relationship), two hydrogen atoms as complex multiplets around 4.1 and 4.95 and one as a doublet at 4.73 (vinyl protons), one hydrogen atom at 5.23 (OH), two hydrogens as a doublet around 6.69 (methylene on an aromatic ring), three hydrogens at 7.79 (methyl on an aromatic ring), and nine hydrogens at 8.66 (*t*-butyl). The final proof of the structure of XII was its synthesis *via* a Claisen rearrangement of the ether XIII.



XIII



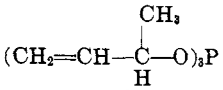
XIV

The phenol XII is undoubtedly formed by loss of a *t*-butyl group from the initially formed ketone XIV. Loss of a *t*-butyl group from the angular position of an *o*-cyclohexadienone has been found to occur under very mild conditions, including chromatography on alumina or silica gel.[4]

Tri-2-butenyl phosphite (XV) reacts with VI very much as does triallyl phosphite. In addition to a 12% yield of ether VII (R = $CH_2CH{=}CHCH_3$) and a 25% yield of phenol VII (R = H), a 13% yield of ketone

$(CH_3CH{=}CH{-}CH_2O)_3P$

XV



$(CH_2{=}CH{-}\overset{CH_3}{\underset{H}{C}}{-}O)_3P$

XVI

XI (R = $CH_2CH{=}CHCH_3$) and a 42% yield of phenol XII (R = $CH_2CH{=}CHCH_3$) were obtained. The n.m.r. spectra of the ether, ketone, and *o*-butenylphenol all clearly showed the presence of the methylene, methyl, and *trans*-vinylic hydrogens of the unrearranged 2-butenyl group.

Reaction of tri-1-methylallyl phosphite (XVI) with VI, however, proceeded rather differently. A somewhat higher yield (34%) of phenol VII (R = H) was obtained, but no phenol resulting from *ortho* alkylation of the phenoxide ion could be detected. A 10% yield of ether VII (R = $CH_3\overset{|}{C}HCH{=}CH_2$) was obtained. The presence of the unrearranged

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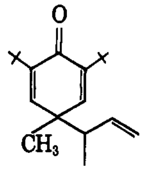
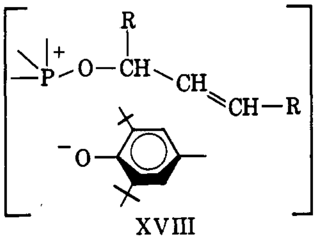
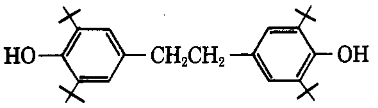
[4] B. Miller and H. Margulies, unpublished work.

1-methylallyl group in VII was obvious from the n.m.r. spectrum, which clearly showed the presence of three vinyl protons, one allylic proton, and one methyl group as a doublet around τ 8.8 (fortunately distinct from the *t*-butyl group at τ 8.64). The major product of the reaction (37%) was the ketone resulting from alkylation of the phenoxide ion at the *para* position. Instead of the expected ketone XVII, however, the ketone obtained was XI (R = $CH_2CH{=}CHCH_3$), identical with that obtained from the reaction of VI with tri-2-butenyl phosphite. Of the two alkylation products, therefore, *the ether was obtained with complete retention of the initial 1-methylallyl system, while the ketone was obtained with complete rearrangement of that system.* This remarkable result may be due to the orientation of the components of the ion pair prior to alkylation of the phenoxide ion. If it is assumed that the ion pair will adopt the structure which will allow closest approach of the phosphorus atom to the oxygen atom of the phenoxide ion (structure XVIII), inspection of molecular models shows that the *para* position of the aromatic ring will be approximately equidistant from the α- and γ-positions of the allyl group. Attack might occur at either position, therefore, and the location of substituents on the allyl group would play a predominant role in deciding the actual site of the reaction. In contrast, the oxygen atom of the phenolate ion can only attack the α-position of the allyl group, unless the ion pair undergoes a substantial change in structure. The ether, therefore, is formed without allylic rearrangement.


XVII

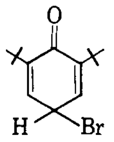

XVIII

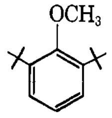
In addition to the alkylation products discussed above, a small yield (*ca.* 6%) of the bisphenol XIX was obtained from the reaction of tri-1-methylallyl phosphite with VI. The origin of XIX is unknown.

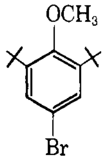

XIX

Reaction of Trimethyl Phosphite with XX.—The complete absence of any C-phosphorylated products (such as V) from the reaction of VI with phosphites is rather surprising, since the work of Borowitz and Virkhaus[5] has shown that bromophosphonium salts can attack enolate ions at carbon as well as oxygen. Steric effects might well prohibit such reactions, however, since all the reactive carbon atoms of the phenoxide ion are tertiary, and presumably well shielded from attack by a tetrasubstituted bromophosphonium ion.

To test this point, the reaction of trimethyl phosphite with 4-bromo-2,6-di-*t*-butylcyclohexadien-1-one (XX)[6] was examined. The reaction product was a mixture of four components: 2,6-di-*t*-butylphenol, 4-bromo-2,6-di-*t*-butylphenol (the tautomeric form of XX), and the corresponding ethers, XXI and XXII.


XX


XXI


XXII

No evidence for the presence of C-phosphorylated products, or of C-alkylated products, could be found.

The surprising appearance of the brominated ether XXII, as well as the large amounts of phenols produced, might be explained by either of two possible paths (Scheme I).

In path A both XXI and XXII arise from attack of phosphite exclusively on bromine. The phenoxide ion formed can either react with a bromophosphonium ion to give XXI, or abstract a proton from XX to give a more stable brominated phenoxide ion, which yields XXII on methylation.

In path B, XXI and XXII are formed by competing abstraction of either protons or positive bromine ions from XX by phosphite molecules.

These paths can be distinguished experimentally. Since the product-determining step in path B is the initial reaction of phosphite with XX, the ratio of products should be independent of the concentrations of reactants, provided that the reasonable assumption that this reaction is first order in XX and in phosphite is correct. The nature of the products formed from path A, on the other hand, should be markedly affected by the concentrations of reagents, since the nature of the products will be determined by the relative rates with which a 2,6-di-*t*-butylphenoxide ion attacks a bromophosphonium ion and a molecule of XX.

Rapid addition of trimethyl phosphite to XX gave XXI and XXII in a mole ration of 55:45 (by v.p.c.). Slow addition of the phosphite to XX changed the ratio of 45:55, while slow addition of XX to the phosphite changed the ratio to 79:21. These results agree with those expected of path A, since high concentrations of dienone relative to phosphite should favor abstraction of a proton from the dienone over abstraction of a methyl group from a bromophosphonium ion.

Reaction of VI with Triphenyl Phosphite.—The reactions of triphenyl phosphites with 4-bromocyclohexadienones normally yield tetraaryloxy phosphonium bromides.[2,3] Since the presence of *t*-butyl groups adjacent to the carbonyl group prevents phosphorylation of the oxygen atom of VI by trialkyl phosphites, it seemed likely that the same could be true of the even more hindered triaryl phosphites. If that were

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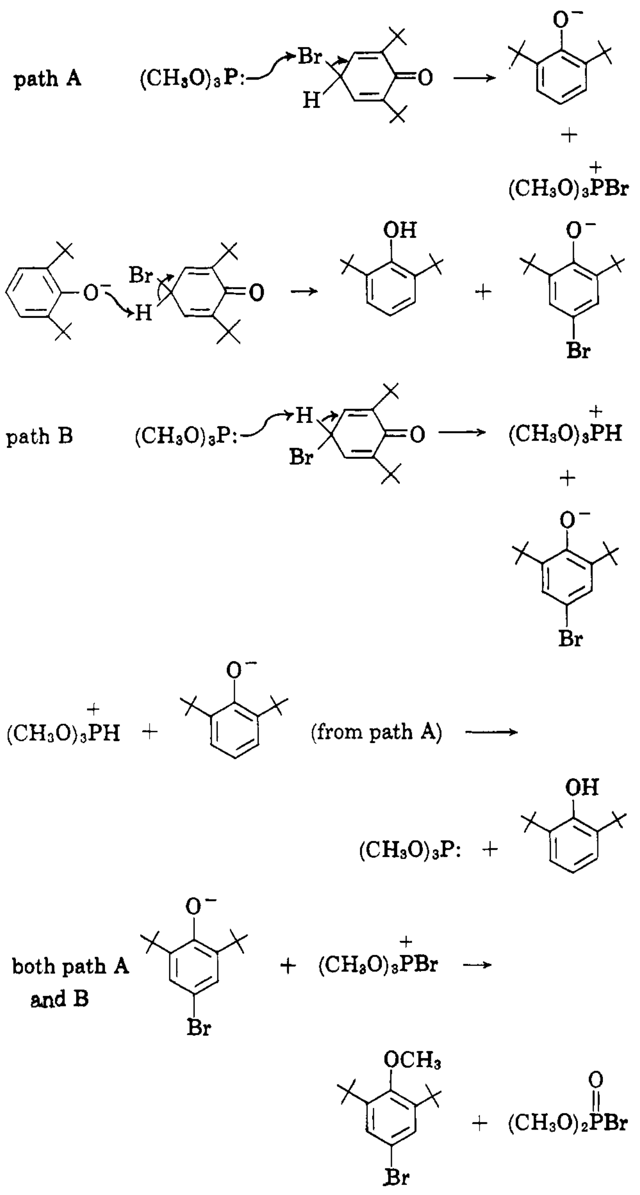
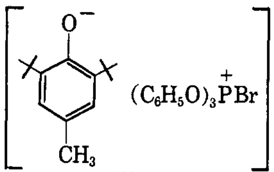
[5] I. J. Borowitz and R. Virkhaus, *J. Am. Chem. Soc.*, **85**, 2183 (1963).

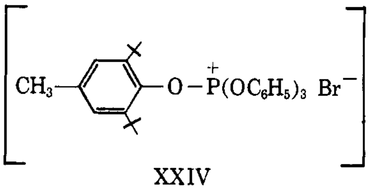
[6] V. V. Ershov and A. A. Volod'kin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 680 (1962).

SCHEME I

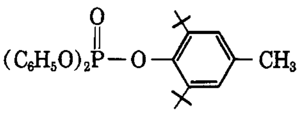


so, the phosphonium salt obtained from reaction of triphenyl phosphite with VI would have the unusual structure XXIII, rather than the structure XXIV which would be expected by analogy with the reaction of triphenyl phosphite with other 4-bromocyclohexadienones.


XXIII


XXIV

Triphenyl phosphite reacted rather slowly with VI, but after 48 hr. at room temperature, an oil separated, which crystallized on standing in the ice box. The deliquescent solid obtained decomposed on solution in water or other hydroxylic solvents. Solution in methanol gave a mixture which contained phenol and XXV. No VII (R = H) could be detected by v.p.c.


XXV

The initial salt, therefore, must have had structure XXIV therefore, rather than XXIII, in spite of the strained structure of XXIV. It is interesting that hydrolysis of XXIV results in elimination of a phenol molecule rather than a molecule of VII (R = H), since ejection of VII would presumably result in appreciable relief of steric strain in the transition state. This suggests that the phenolate ion bears appreciable negative charge in the transition state for its elimination, and that the most stable anion is eliminated.

Experimental[7]

Preparation of 2-Bromo-6-*t*-butyl-4-methylphenol.—A solution of 2-*t*-butyl-4-methylphenol (143.0 g., 0.935 mole) in 500 ml. of glacial acetic acid was cooled in an ice bath and stirred while bromine (47.7 ml., 0.935 mole) was added. At the end of the addition (15 min.) water was added. The organic layer was dissolved in methylene chloride, washed with sodium bicarbonate solution, then with water, and dried over magnesium sulfate; the solvent was evaporated to give 217.0 g. (0.935 mole, 100%) of 2-bromo-6-*t*-butyl-4-methylphenol as a brown fluid. A 75.0-g. sample was distilled, b.p. 115–118° (2.5 mm.), to give 73.4 g. of pale yellow fluid, identical in infrared spectrum with the undistilled product.

Anal. Calcd. for $C_{11}H_{15}BrO$: C, 54.3; H, 6.17. Found: C, 54.8; H, 6.23.

Preparation of 2,4-Dibromo-6-*t*-butyl-4-methylcyclohexadien-1-one (A).—A solution of 2-bromo-6-*t*-butyl-4-methylphenol (distilled, 47.5 g., 0.205 mole) in 300 ml. of glacial acetic acid was cooled in an ice bath and stirred. Ice (*ca.* 50 g.) was added. Bromine (10.4 ml., 0.204 mole) was added drop by drop. At the end of the reaction a second liquid phase had separated. An additional 100 ml. of water containing some ice was added, and the organic layer was extracted with methylene chloride, and was dried over magnesium sulfate (while being kept in an ice bath). Evaporation of the solvent left 62.8 g. (0.202 mole, 99%) of an orange liquid. Its infrared spectrum showed an intense carbonyl peak at 6.0 μ and a very small phenol peak at 2.8 μ.

Reaction of A with Trimethyl Phosphite.—A solution of 2,4-dibromo-6-*t*-butyl-4-methylcyclohexadien-1-one (12.5 g., 0.0402 mole) in 50 ml. of benzene was cooled in ice and a solution of trimethyl phosphite (5.0 g., 0.0403 mole) in 10 ml. of benzene was added. A vigorous reaction ensued immediately The benzene boiled gently, and the orange color of the solution changed to a light yellow. Evaporation of the solvent left 15.8 g. of yellow oil which was chromatographed on neutral alumina (activity I) to give 10.0 g. of a pale yellow oil. Molecular distillation at 0.025 mm. and a pot temperature of 95–125° gave 8.60 g. (0.0245 mole, 61%) of dimethyl 2-bromo-6-*t*-butyl-4-methylphenyl phosphate as a pale oil which crystallized on standing. Recrystallization from heptane gave colorless plates, m.p. 55–57°.

Anal. Calcd. for $C_{13}H_{20}BrO_4P$: C, 44.5; H, 5.69; Br, 22.8; P, 8.84. Found: C, 45.1; H, 5.96; Br, 22.9; P, 8.89.

Reaction of Trimethyl Phosphite with 4-Bromo-2,6-di-*t*-butyl-4-methylcyclohexadien-1-one (VI).—To a solution of 8.70 g. of VI (0.0291 mole) in 30 ml. of anhydrous benzene was added a solution of 3.72 g. (0.030 mole) of trimethyl phosphite in 2 ml. of benzene. A green color developed after a few seconds and the

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(7) Microanalyses were by Galbraith Laboratories, Knoxville, Tenn. All melting points are corrected. All boiling points are uncorrected.

solution became warm but did not reflux. After 3 min., the green color faded to a pale yellow. Evaporation of the solvent left 12.1 g. of yellow oil, which was chromatographed on 500 g. of neutral alumina (activity I). Elution with petroleum ether gave 5.27 g. (0.226 mole, 79%) of 2,6-di-*t*-butyl-4-methylphenyl methyl ether,[8] n^{25}_{D} 1.5005. Elution with methylene chloride gave 0.98 g. (15%) of 2,6-di-*t*-butyl-4-methylphenol.

The reaction between VI and triethyl phosphite was carried out in the same manner to give 70% of 2,6-di-*t*-butyl-4-methylphenyl ethyl ether as a colorless liquid, n^{25}_{D} 1.4978.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.3; H, 11.3. Found: C, 82.9, 82.7; H, 11.9, 11.9.

The reaction between VI and triisopropyl phosphite gave a 22% yield of 2,6-di-*t*-butyl-4-methylphenyl isopropyl ether as a colorless fluid, n^{25}_{D} 1.4960.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.5; H, 11.5. Found: C, 82.9, H, 11.7.

Tri-1-methylallyl phosphite (XVI) and tri-2-butenyl phosphite (XV) were prepared as described by Pudovik.[9] **Caution**: XVI was prepared twice using dimethylaniline as a catalyst without incident. When pyridine was used as a catalyst, the product decomposed violently on distillation, and, on one occasion, on standing at room temperature after removal of solvent.

Reaction of VI with Tri-1-methylallyl Phosphite (XVI).—A suspension of VI (12.0 g., 0.0402 mole) in 25 ml. of benzene was cooled in ice and tri-1-methylallyl phosphite (10.0 g., 0.0410 mole) was added. The mixture immediately turned orange and then red. The solid VI dissolved. After standing for 15 min., the benzene was removed under vacuum, and the residue was chromatographed on 1.5 lb. of Woelm neutral alumina (activity II). Elution with petroleum ether gave 1.4 g. (0.0051 mole, 13%) of 2,6-di-*t*-butyl-4-methylphenyl 1-methylallyl ether.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.2; H, 10.95. Found: C, 82.8; H, 10.6.

Further elution with petroleum ether and then methylene chloride gave a mixture, which on a second chromatography gave 4.1 g. (0.0150 mole, 37%) of 2,6-di-*t*-butyl-4-methyl-4-(2-butenyl)cyclohexadien-1-one, identical with the product of the reaction of VI with tri-2-butenyl phosphite, and 2.7 g. (0.0123 mole, 31%) of 2,6-di-*t*-butyl-*p*-cresol. Further elution of the original chromatography column with chloroform, and finally with methanol, gave 0.50 g. (0.0014 mole, 6%) of 1,2-di(3,5-di-*t*-butyl-4-hydroxyphenyl)ethane, m.p. 174–175° (lit.[10] m.p. 173–175°).

Reaction of VI with tri-2-butenyl phosphite (XV) was carried out in the same manner. The products of the reaction, in the order eluted from an alumina column, were (a) **2-butenyl 2,6-di-*t*-butyl-4-methylphenyl ether** (16%), m.p. 57–61° from hexane (*Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.3; H, 10.9. Found: C, 83.4; H, 11.1); (b) **2,6-di-*t*-butyl-4-(2-butenyl)-4-methylcyclohexadien-1-one** (14%) (*Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.3; H, 10.95. Found: C, 83.3; H, 11.1); (c) **2,6-di-*t*-butyl-*p*-cresol** (20%); and (d) **2-(2-butenyl)-6-*t*-butyl-*p*-cresol** (42%) (*Anal.* Calcd. for $C_{15}H_{22}O$: C, 82.6; H, 10.1. Found: C, 82.1; H, 10.3).

The reaction of VI with triallyl phosphite was carried out similarly. The products of the reaction, in the order they were eluted from the column, were (a) **allyl 2,6-di-*t*-butyl-4-methylphenyl ether** (18%), n^{25}_{D} 1.5051 (*Anal.* Calcd. for $C_{18}H_{28}O$: C, 83.1; H, 10.8. Found: C, 83.5; H, 11.0); (b) **4-allyl-2,6-di-*t*-butyl-4-methylcyclohexadien-1-one** (19%) (*Anal.* Calcd. for $C_{18}H_{28}O$: C, 83.1; H, 10.8. Found: C, 82.9; H, 10.5); (c) **2,6-di-*t*-butyl-*p*-cresol** (25%); and (d) **2-allyl-6-*t*-butyl-*p*-cresol** (38%) (*Anal.* Calcd. for $C_{14}H_{20}O$: C, 82.4; H, 9.81. Found: C, 82.1; H, 10.1).

Preparation of Allyl 2-*t*-Butyl-4-methylphenyl Ether.—Allyl bromide (24.2 g., 0.20 mole) was added to a solution of 2-*t*-butyl-*p*-cresol (32.8 g., 0.20 mole) and 11.2 g. (0.20 mole) of potassium hydroxide in 200 ml. of water and 125 ml. of ethanol. The mixture was stirred for 19 hr. at room temperature. Additional ethanol (75 ml.) was added, and stirring was continued for an additional 24 hr. The reaction mixture was extracted with methylene chloride, the methylene chloride was evaporated, and the residue was chromatographed on Woelm neutral alumina (activity I). Elution with petroleum ether gave 1.5 g. (0.0074 mole, 4%) of allyl 2-*t*-butyl-4-methylphenyl ether.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.3; H, 10.0. Found: C, 82.5; H, 9.99.

An additional 1.9 g. of ether containing *ca.* 10% of 2-*t*-butyl-*p*-cresol was obtained by further elution with petroleum ether.

Claisen Rearrangement of Allyl 2-*t*-Butyl-4-methylphenyl Ether.—A solution of allyl 2-*t*-butyl-4-methylphenyl ether (1.0 g., 0.0049 mole) in 3 ml. of N,N-diethylaniline was refluxed for 1.5 hr. The solution was then cooled, washed with aqueous hydrochloric acid, and extracted with methylene chloride, and the organic layer was washed with sodium bicarbonate, dried, and evaporated to give 0.40 g. (0.0020 mole, 40%) of 2-allyl-6-*t*-butyl-*p*-cresol, identical in infrared spectrum and v.p.c. retention time (silicone gum column) with that previously described.

Reaction of Trimethyl Phosphite with 4-Bromo-2,6-di-*t*-butylcyclohexadien-1-one (XX).—To a solution of 4-bromo-2,6-di-*t*-butylcyclohexadien-1-one[6] (13.0 g., 0.0456 mole) in 25 ml. of benzene was added a solution of trimethyl phosphite (5.66 g., 0.0456 mole) in 10 ml. of benzene. The solution became noticeably warm after a few seconds, and reaction was complete in 1–2 min. The solvent was evaporated, and the oily residue was chromatographed on 1.5 lb. of neutral alumina (activity I). Elution with petroleum ether gave 5.5 g. of a mixture of ethers. Further elution with petroleum ether gave 4.5 g. (0.0218 mole, 48%) of 2,6-di-*t*-butylphenol. Finally, elution with methylene chloride gave 0.6 g. (0.0021 mole, 5%) of 4-bromo-2,6-di-*t*-butylphenol. Distillation of the ether fraction gave two components. The first component was 2,6-di-*t*-butylanisole (2.5 g., 0.011 mole, 24%), b.p. 105–107 (3.5 mm.), n^{25}_{D} 1.5046.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.8; H, 10.9. Found: C, 81.4; H, 10.5.

A second component, b.p. 122–125°, n^{25}_{D} 1.5283, was shown to be 4-bromo-2,6-di-*t*-butylanisole (1.8 g., 0.0060 mole, 14%) by comparison with a synthetic sample

V.p.c. of the ether-containing fraction before distillation (6-ft. silicone rubber column, 180°) showed it to contain 2,6-di-*t*-butylanisole and 4-bromo-2,6-di-*t*-butylanisole in a molar ratio of 55:45.

Another run was carried out in the same manner except that the phosphite was added drop by drop, over a 15-min. period, to the reaction mixture. V.p.c. of the ether fractions showed the molar ratio of 2,6-di-*t*-butylanisole and 4-bromo-2,6-di-*t*-butylanisole to be 45:55.

In a third run, the solution containing the dienone was added slowly to the solution containing the phosphite. V.p.c. showed the ratio of 2,6-di-*t*-butylanisole to 4-bromo-2,6-di-*t*-butylanisole to be 79:21. The yield of 2,6-di-*t*-butylphenol isolated by chromatography on neutral alumina was 14%.

Preparation of 4-Bromo-2,6-di-*t*-butylanisole.—Sodium hydride (0.43 g., 0.018 mole) was dissolved in 150 ml. of DMSO, and 4-bromo-2,6-di-*t*-butylphenol (5.0 g., 0.017 mole) was added. Methyl iodide (20 g., 0.14 mole) was added, and the solution was allowed to stand at room temperature for 3 hr. Methylene chloride was added, and the mixture was washed three times with water and dried over magnesium sulfate. The solvent was evaporated to give 3.6 g. of dark brown oil, which was chromatographed on neutral alumina. Elution with petroleum ether gave 2.9 g. (0.0097 mole, 57%) of 4-bromo-2,6-di-*t*-butylanisole as a colorless liquid, which solidified on standing, m.p. 49–50°.

Anal. Calcd. for $C_{15}H_{23}BrO$: C, 60.2; H, 7.74; Br, 26.5. Found: C, 60.1; H, 7.78; Br, 26.8.

Reaction of VI with Triphenyl Phosphite.—To a solution of VI (5.00 g., 0.0197 mole) in 50 ml. of benzene was added 6.20 g. (0.0200 mole) of triphenyl phosphite. On standing overnight at room temperature, a second, oily phase appeared at the bottom of the flask. This crystallized on standing in the ice box for 4 days. The mixture was filtered under nitrogen in a drybox, and the solid was washed several times with anhydrous benzene. The product obtained was 3.4 g. (28%) of light yellow crystals which rapidly turned to oil on exposure to air. A small sample was dissolved in methanol and analyzed on a 6-ft. diethylene glycol succinate column at 150°. The only detectable product was phenol. The solid was dissolved in water and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with dilute sodium hydroxide solution, dried over magnesium sulfate, and evaporated to give 2.3 g. (0.00508 mole, 26%) of 2,6-di-*t*-butyl-4-methylphenyl diphenyl phosphate as a light yellow oil which crystallized when scratched in an ice

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[8] L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957). The author thanks Dr. Cohen for supplying an infrared spectrum of 2,6-di-*t*-butyl-4-methylphenyl methyl ether.

[9] A. N. Pudovik, *Zh. Obshch. Khim.*, **27**, 2755 (1957).

[10] G. M. Coppinger, *J. Am. Chem. Soc.*, **79**, 2758 (1957).

bath. Recrystallization from ether gave a white powder, m.p. 138–139°.

Anal. Calcd. for $C_{27}H_{33}O_4P$: C, 71.6; H, 7.31; P, 6.86. Found: C, 72.2, 71.9; H, 7.58, 7.11; P, 6.75, 6.92.

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Some New Tricyclic Compounds Containing the Bispidine Moiety

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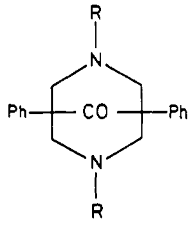
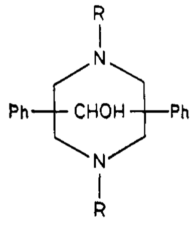
The reaction of 1,5-diphenyl-3,7-bis(chloroacetyl)-9-bispidinone (Ic) with ammonia and primary amines has resulted in the formation of a new series of triazatricyclotetradecanes (III). The tertiary amino nitrogen in the 4-position of the new ring system has been shown to be weakly basic. The same behavior of N-4 is observed with the tricyclic compounds, IV, obtained from the reaction of 1,5-diphenyl-3,7-bis(chloroacetyl)-9-bispidinol (IIb) with primary amines. This lack of basicity coupled with n.m.r. studies has permitted a conformational assignment of these tricyclic compounds.

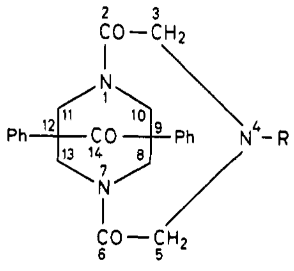
Both the chemical and the pharmacological interest of compounds related to 1,5-diphenyl-9-bispidinone (Ia) and 1,5-diphenyl-9-bispidinol (IIa) have led us to undertake the synthesis of new substances belonging to this class of compounds. In a recent publication,[2] we described the synthesis of a series of 1,5-diphenyl-3,7-bis(aminoacetyl)-9-bispidinones from the reaction of the corresponding bis(chloroacetyl) compound, Ic, with secondary amines. These compounds displayed the expected physical and chemical properties of tertiary amines including solubility in weak acids and formation of bisquaternary salts.[3] However, when the corresponding reaction was carried out with ammonia or primary amines, the resulting products were only sparingly soluble in most organic solvents, melted or decomposed at temperatures about 250–300°, and displayed only weakly basic properties. These physical properties coupled with the microanalytical data and molecular weight determinations (see Table I) suggested the formation of the tricyclic system III.



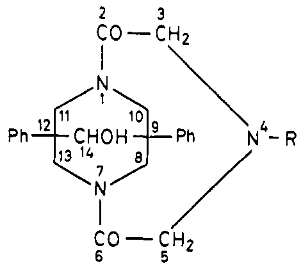
I a, R = H
b, R = $COCH_3$
c, R = $COCH_2Cl$



II a, R = H
b, R = $COCH_2Cl$

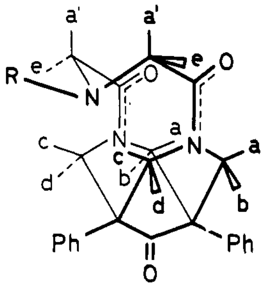


III a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = CH_2CH_2OH
e, R = $CH_2C_6H_5$
f, R = $COCH_3$

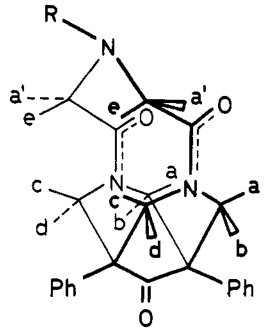


IV a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = CH_2CH_2OH
e, R = $CH_2C_6H_5$
f, R = $COCH_3$

This new tricyclic system has a very rigid and compact steric structure. Dreiding models show that rotation is allowed only about the C-3–N-4–C-5 bridge resulting in two possible conformations, A and B. The tertiary amines, compounds IIIb–e, form hydrochlorides which hydrolyze immediately in the presence of water. Attempted preparation of the methiodide in Methyl Cellosolve with excess methyl iodide failed. These properties indicated that conformation A is preferred since axial substitution to form a quaternary salt should result in strong steric interaction with the two H_c hydrogens. As expected, equatorial substitution, both alkylation and acylation, of the secondary amino function of compound IIIa was readily effected. Methylation with excess methyl iodide in refluxing Methyl Cellosolve gave as the exclusive product the same tertiary amine, IIIb, as was obtained by the cyclization reaction with methylamine. Acetylation under mild conditions led to the N-acetyl derivative, IIIf, in high yield. An examination of Dreiding models lends additional support to this assignment. The model of conformation B reveals a strong steric interaction between protons H_c and H_e which lie in the same plane at a calculated distance of 1.5 Å.



A



B

A close analysis of the n.m.r. spectrum[4] of compound IIIb (Figure 2) completely justifies the above interpretation. In order to better understand this spec-

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[1] Communications should be addressed to G. Settimj, Istituto Superiore di Sanità, Viale Regina Elena 299, Rome.

[2] S. Chiavarelli and G. Settimj, *Gazz. chim. ital.*, **88**, 1253 (1958).

[3] S. Chiavarelli and G. Settimj, unpublished results.

[4] Spectra were taken in deuteriochloroform using a Varian Model A60 spectrometer. Decoupling experiments were performed with the Varian Model HR60 spectrometer. Tetramethylsilane (TMS) served as internal standard.