Phosphorus Derivatives of Nitrogen Heterocycles. I. Preparation and Chemistry of 9,10-Dihydroacridinephosphonic Acid Derivatives

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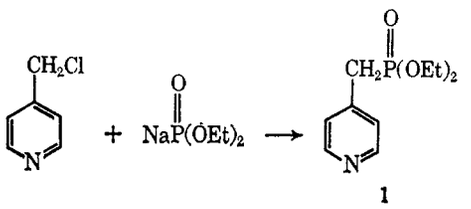
The reaction of N-methylacridinium quaternaries or acridinium salts with diethyl sodiophosphonate gives diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**10**) and diethyl 9,10-dihydroacridine-9-phosphonate (**14**). Dehydrogenation of **14** yields diethyl acridine-9-phosphonate (**22**). Dihydroacridinephosphonate **10** forms an anion which is alkylated with alkyl halides and which undergoes the Wadsworth–Emmons reaction with aryl aldehydes to produce olefins **15**, **16**, and **17**. Upon reaction with Grignard reagents, **10** undergoes an unusual rearrangement reaction to produce ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (**28**).

Very few compounds are known in which phosphorus is attached directly to a nitrogen heterocycle as a ring substituent. Diethyl acridine-9-phosphonate has been described as the product from the Arbusov reaction between 9-chloroacridine and triethyl phosphite.[1] The Arbusov reaction of 2,4-diamino-6-chloro-1,3,5-triazine with triethyl phosphite is reported to give the corresponding 6-phosphonate.[2] Closely related phosphonic acid derivatives are the products of the reactions between halomethylpyridines and quinolines with diethyl sodiophosphonate.[3-5] For example, 4-chloromethylpyridine on reaction with diethyl sodiophosphonate yields diethyl (4-pyridyl)methylphosphonate (**1**).[4]



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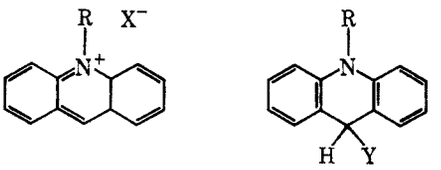
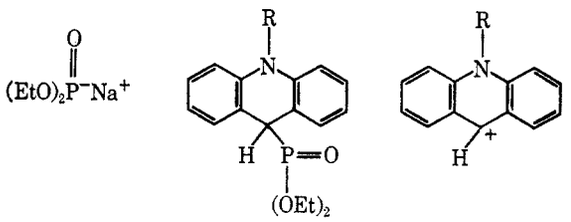
The present paper describes part of a study designed to produce additional examples of phosphorus derivatives of nitrogen heterocycles.

It has long been known[6-8] that N-alkyl- or N-arylacridinium salts, such as halides, when treated with nucleophilic anions are converted into nonionic compounds. Thus, an aqueous solution of N-phenylacridinium iodide (**2**) when treated with sodium hydroxide gives the nonionic 9-hydroxy compound **3**. The dihydroacridine **3** can be reconverted into the ionic form (**2**) by reaction with dilute hydrochloric acid. 9-Cyanodihydroacridines **5** can be prepared from N-alkylacridinium salts **4** with aqueous potassium cyanide. The cyano compounds **5** are more stable than the hydroxy compounds **3** necessitating heating with strong acid in order to be converted to the ionic derivative **4**. It therefore appeared that the strong nucleophile **6**, the anion from diethyl hydrogen phosphonate, should react with an acridinium quaternary salt to form a stable dihydroacridine-9-phosphonate **7**. In terms of Pearson's concept of hard and soft acids and bases the structure **7** should be stable, being a combination of the acridine cation **8**, a soft acid, and the anion **6**, a soft base.[9]



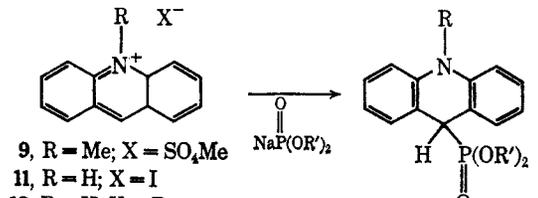
2, R = Ph; X = Cl
4, R = alkyl; X = Cl

3, R = Ph; Y = OH
5, R = alkyl; Y = CN



6 **7** **8**

When N-methylacridinium methosulfate (**9**) was treated with diethyl sodiophosphonate, diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**10**) was formed in good yield. The assigned structure was fully confirmed by the spectroscopic data obtained and by the chemical properties. In particular the nuclear magnetic resonance (nmr) spectrum of **10** showed absorption for the phosphonate ester groups at δ 1.13 and 3.83, the N-methyl group at 3.32, and H at C_9 as a doublet at 4.5 (J_{PCH} = 26 Hz). The relative peak areas and additional absorption from the aryl protons were in accord with the structural assignment. The infrared (ir) spectrum showed characteristic phosphonate absorptions at 1250 (P=O) and 1030–1040 cm^{-1} (POC). The ultraviolet (uv) spectrum with absorption at 287 mμ was fully consistent with a dihydro-



9, R = Me; X = SO_4Me
11, R = H; X = I
13, R = H; X = Br

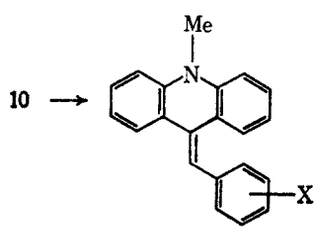
10, R = Me; R′ = Et
12, R = Me; R′ = *i*-Pr
14, R = H; R′ = Et

(1) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 1002 (1947).
(2) G. F. D'Alelio, U. S. Patent 3,011,998 (1961).
(3) P. Bednarek, R. Bodalski, J. Michalski, and S. Musierowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **11**, 507 (1963).
(4) E. Maruszewska-Wieczorkowska and J. Michalski, *Rocz. Chem.*, **38**, 625 (1964).
(5) R. Bodalski, A. Malkiewicz, and J. Michalski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **13**, 139 (1965).
(6) A. Albert, "The Acridines," 2nd ed, Edward Arnold, Ltd., London, 1966, p 332.
(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, pp 575–586.
(8) A. Hantzsch and M. Kalb, *Chem. Ber.*, **32**, 3109 (1899).
(9) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

acridine chromophore. The phosphonate **10** showed good thermal stability being recovered unchanged after heating at 200° for 1 hr. In an analogous manner the acridinium salt **9** yielded diisopropyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**12**) when treated with diisopropyl sodiophosphonate.

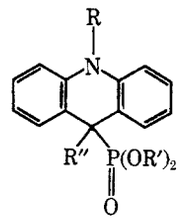
Acridine hydrobromide **13** or hydroiodide **11** underwent the same reaction as the quaternary salts to produce diethyl 9,10-dihydroacridine-9-phosphonate (**14**) in 70% yield. The nmr spectrum of **14** was very similar to that of the homolog **10** except for the absence of the N-methyl peak. The ir spectrum showed NH absorption (3230 cm^{-1}) and weakly hydrogen-bonded P=O (1230 cm^{-1}). It appears that the reaction of the acridine salts and quaternaries with dialkyl sodiophosphonates to produce dihydroacridinephosphonates is quite general, the availability of the acridine quaternaries being the main limitation.

These compounds undergo reactions typical of phosphonic acid esters, thereby providing further support for the structural assignments made above. The hydrogen at C_9 is particularly acidic, being activated by the phosphonate ester group and being at the same time doubly benzylic. The anion is thus readily formed by treatment with base. The phosphonate **10** yields the expected anion with sodium hydride in dimethoxyethane, and the anion reacts with benzaldehyde in a Wadsworth–Emmons reaction[10] to give 10-methyl-9-benzylidene-9,10-dihydroacridine (**15**). The structure of this product was confirmed by an independent synthesis, involving reaction of N-methylacridone with benzyl magnesium bromide.[11] *m*-Nitrobenzaldehyde and *p*-methoxybenzaldehyde likewise give substituted benzylidene derivatives of 9,10-dihydroacridines **16** and **17**. These compounds appear



15, X = H
16, X = *m*-NO_2
17, X = *p*-OMe

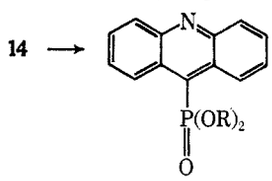
to be more stable in moist air than the earlier literature indicates.[12] However, when pyridine-2-carboxaldehyde was allowed to react with the anion of the phosphonate **10** N-methylacridone was the main product, presumably arising from hydrolytic degradation of the olefin during work-up.[12] The carbanions of the phosphonates **10** and **14** were alkylated by standard procedures.[13] Thus the anion of **10** reacted readily with methyl iodide to give diethyl 9,10-dimethyl-9,10-dihydroacridine-9-phosphonate (**18**). With the NH dihydroacridines the possibility of forming dianions exists so that **14** treated with 2 equiv of butyllithium followed by excess methyl iodide gave the dimethylated



18, R = Me; R′ = Et; R″ = Me
19, R = CH_2Ph; R′ = Et; R″ = CH_2Ph
20, R = H; R′ = Et; R″ = CH_2Ph
21, R = Me; R′ = Et; R″ = Et

product **18** identical with that prepared from the N-methyl compound **10**. This same dianion upon reaction with exactly 2 equiv of benzyl bromide afforded two products in 47 and 20% yields, respectively. The minor product was readily shown to be the 9,10-dibenzyl derivative **19** from the analytical data and particularly the nmr spectrum. The major product was shown to be the mono-C-benzylated compound **20** by its analysis and nmr spectrum. In the nmr spectrum of **20** the benzyl protons appeared as a doublet (J_{PH} = 8 Hz), while the characteristic doublet for H at C_9 was absent confirming C-benzylation. The ir spectrum of this monobenzyl compound showed the expected N—H stretching absorption. It was not possible to detect any N-monobenzylated material in the reaction product.

Further chemical characterization of these dihydroacridine derivatives is provided by the results of the dehydrogenation of **14**. Upon heating in benzene with tetrachloro-*p*-benzoquinone, the dihydroacridine **14** afforded, after chromatography on alumina, diethyl acridine-9-phosphonate (**22**), mp 95–96°. The nmr



22, R = Et
23, R = H

spectrum, Figure 1, is particularly informative, providing substantiation for the assigned acridine phosphonic acid structure. The multiplet centered at δ 4.25 is assigned to the ester methylene protons and arises from spin coupling with both the methyl protons and phosphorus and is fairly typical of phosphonate ethyl esters.[14,15] The other assignments are straightforward and are indicated in Figure 1. The uv spectrum with maxima at 269, 255, and 210 mμ indicates the presence of the acridine chromophore.[16] This structure had previously been assigned to the product, mp 165–167°, of the Arbusov reaction between 9-chloroacridine and triethyl phosphite.[1] Characterization of the product previously reported was not complete, however, and the product may not, in fact, contain phosphorus. Hydrolysis of the acridine phosphonate **22** with 18% hydrochloric acid gave acridine-9-phosphonic acid (**23**). The acid was insoluble in

(10) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(11) E. D. Bergmann, M. Rabinovitz, and A. Bromberg, *Tetrahedron*, **24**, 1289 (1968); H. Decker and R. Pschorr, *Chem. Ber.*, **37**, 3396 (1904).

(12) Reference 6, p 340.

(13) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 203–212.

(14) See, for example, J. D. Baldeschwieler, F. A. Cotton, B. D. Nageswara Rao, and R. A. Schunn, *J. Amer. Chem. Soc.*, **84**, 4454 (1962).

(15) The methylene protons in all the dihydroacridinephosphonic acid ethyl esters examined in this work give the more typical approximate quintets in their nmr spectra.

(16) Reference 6, p 188.

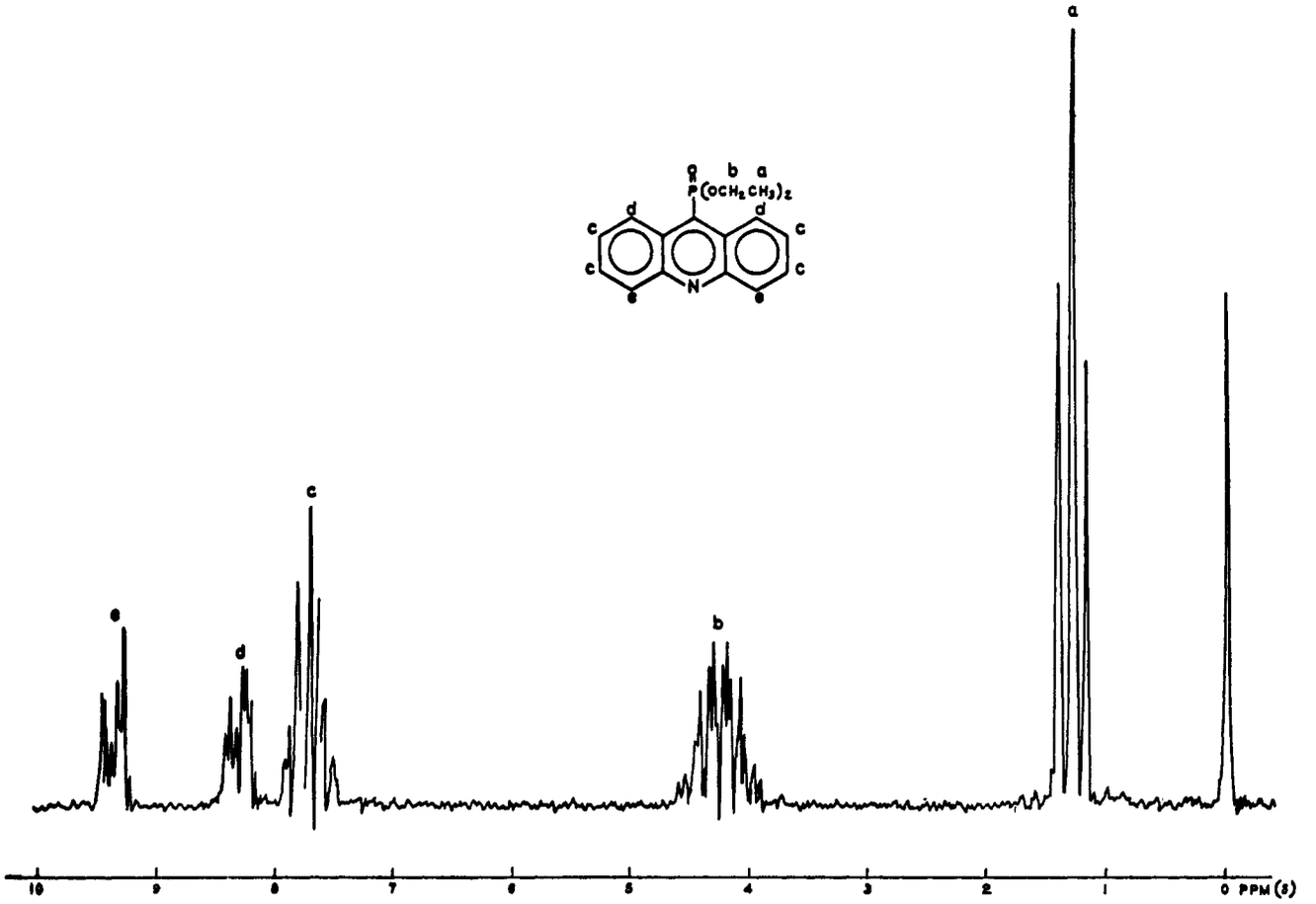
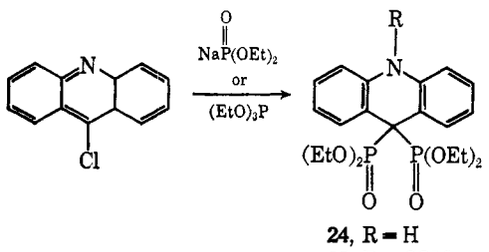


Figure 1.—The nmr spectrum of diethyl acridine-9-phosphonate (22).

common organic solvents but dissolved readily in aqueous base and was reprecipitated upon acidification.

An attempt was made to repeat the Arbusov reaction of 9-chloroacridine and triethyl phosphite under the conditions described by Kosolapoff.[1] No product corresponding to that described by Kosolapoff (mp 165–167°) could be isolated from the reaction. The only materials obtained, after chromatography on alumina, were unreacted chloroacridine and a solid containing phosphorus, mp 211–213°. This compound was the sole product isolated from the reaction of 9-chloroacridine and diethyl sodiophosphonate in dimethylformamide. The ir spectrum of this product showed NH absorption and the uv spectrum suggested the presence of a dihydroacridine chromophore (λ max, 209, 238, 292, and 332 mμ). The nmr spectrum and elementary analysis together with the above spectral data suggest that this compound is tetraethyl 9,10-dihydroacridine-9,9-diphosphonate (**24**). The compound is readily acetylated to produce the acetate (**25**).



24, R = H
25, R = COMe

which exhibits spectral data in complete accord with the structure. It seems probable that the acridinephosphonate **22** is an intermediate in the formation of the diphosphonate **24** from 9-chloroacridine since on heating the phosphonate **22** with diethyl sodiophosphonate in dimethylformamide the diphosphonate **24** is formed in 65% yield. The ease of nucleophilic attack at C_9 in the acridinephosphonate **22** is surprising. These results, however, still leave unanswered the question of the structure of Kosolapoff's product.

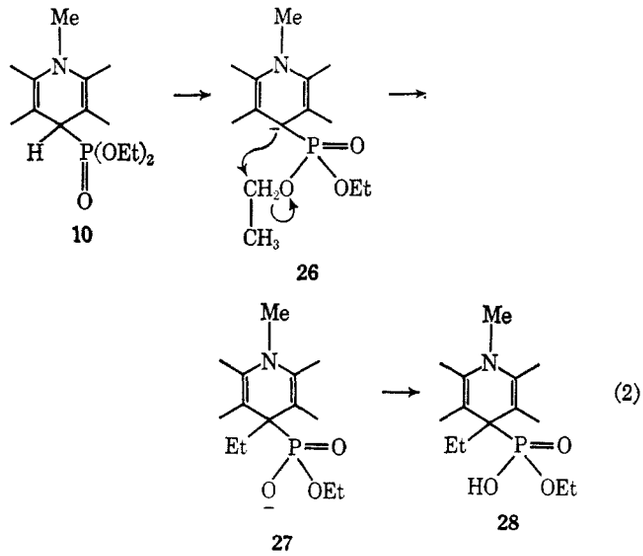
Typical phosphonic acid esters are converted into tertiary phosphine oxides upon treatment with Grignard reagents (eq 1).[17] Upon treatment of the phos-

$$\mathrm{R\overset{O}{\overset{\|}{P}}(OR')_2 + 2R''MgX \longrightarrow R\overset{O}{\overset{\|}{P}}R''_2 + 2MgOR'X} \quad (1)$$

phonate ester **10** with a Grignard reagent an unusual and unexpected isomerization reaction was observed. The product from the reaction with methylmagnesium chloride in ether was shown by nmr and ir spectra not to be the expected tertiary phosphine oxide. It was further found that phenylmagnesium bromide gave an identical product, albeit in lower yield, which suggested an isomerization process initiated by the Grignard reagents. Elementary analysis confirmed that the product was isomeric with the starting material, and titration with base established an equivalent weight of 329. An analysis of the nmr spectrum led to the assignment of the structure of this acid as ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (**28**). The nmr spectrum showed two ethyl

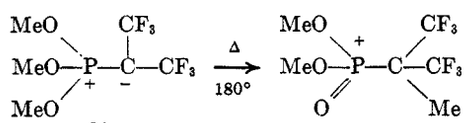
(17) K. D. Berlin, T. H. Austin, M. Peterson, and M. Nagabhushanam in "Topics in Phosphorus Chemistry," Vol. 1, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, New York, N. Y., 1964, pp 39–43.

groups in slightly different envionments, and most significantly the characteristic doublet for H at C_9 was absent. The acidic proton appeared at low field (δ 11.50). The pathway for this isomerization is not certain but probably involves formation of a carbanion at C_9 (**26**) followed by rearrangement (eq 2). The



(2)

driving force here could derive from the greater stability of anion **27** over the anion **26**. The fact that the anion **26** derived by treatment of **10** with Grignard reagent rearranges to **27**, whereas **26** formed from **10** with sodium hydride or butyllithium does not rearrange can be explained by a combination of two factors: (a) the external electrophiles (aryl aldehydes and alkyl halides) added to the sodium- and lithium-derived anions are stronger than the internal phosphonate ester as electrophiles and (b) carbanions show a greater tendency to rearrange in the presence of magnesium salts than in presence of sodium or lithium.[18] This type of rearrangement is almost without precedent, the closest example being the thermal rearrangement of the ylide **29**.[19] The monoester **28** was readily converted into the diethyl ester **21** upon heating with triethyl orthoformate.[20]



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Experimental Section

Melting points are uncorrected and were measured on a Fisher-Johns hot stage melting point apparatus. The elemental analyses were by Clark Analytical Laboratory and Dr. F. J. Ludwig, Petrolite Corp., Physical-Analytical Section. Nmr spectra were obtained with a Varian Associates A-60 spectrometer, using a tetramethylsilane internal standard. Infrared spectra were determined on a Beckman IR-4 spectrometer.

Diethyl 10-Methyl-9,10-dihydroacridine-9-phosphonate (10).—To a stirred suspension of N-methylacridinium methosulfate, derived from acridine (100 g, 0.56 mol) and dimethyl sulfate (70.5 g, 0.56 mol) in toluene (200 ml) was added diethyl sodiophosphonate in dioxane (200 ml) [derived from sodium (12.9 g, 0.56 g-atom) and diethyl phosphite (77.5 g, 0.56 mol)] during 30 min. During the addition, which was carried out under an argon blanket, the reaction temperature rose to 55°. The reaction mixture was heated at 85–90° for 2 hr and, after cooling, water (150 ml) was added. The organic layer was separated, and the aqueous layer was extracted with two 50-ml portions of benzene. The combined organic extracts were dried ($MgSO_4$) and evaporated to yield a green oil. Crystallization from benzene–hexane gave diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**10**), yield 130 g (68%), mp 85–88°. Recrystallization gave an analytically pure sample: mp 89–91°; nmr ($CDCl_3$) δ 1.13 (t, 6, J = 7 Hz, CH_3CH_2), 3.32 (s, 3, NCH_3), 3.83 (m, 4, J = 7 Hz, CH_3CH_2O), 4.5 (d, 1, J = 26 Hz, HCP), 7.4–6.8 (m, 8, Ar-H); ir (Nujol) 1250 (P=O) and 1030–1040 cm^{-1} (P–O–C); uv max (MeOH) 287 mμ (log ϵ 4.16) and 210 (4.72).

Anal. Calcd for $C_{18}H_{22}NO_3P$: C, 65.24; H, 6.69; N, 4.23; P, 9.35. Found: C, 65.04; H, 6.73; N, 4.24; P, 9.32.

Diethyl 9,10-Dihydroacridine-9-phosphonate (14).—To a stirred suspension of acridine hydrobromide (26 g, 0.1 mol) in toluene (100 ml) was added diethyl sodiophosphonate (16 g, 0.1 mol) in dioxane (50 ml) during 15 min under an argon blanket. The reactants were heated under reflux for 2 hr and after cooling water (75 ml) was added. Chloroform (100 ml) was added, and the organic layer was separated. The aqueous layer was extracted with two 50-ml portions of chloroform, and the combined organic fractions were evaporated. Crystallization from benzene–hexane gave diethyl 9,10-dihydroacridine-9-phosphonate (**14**): yield 20 g (63%); mp 189–190°; nmr ($CDCl_3$) δ 1.16 (t, 6, J = 7 Hz, CH_3CH_2O), 3.90 (m, 4, J = 7 Hz, CH_3CH_2O), 4.55 (d, 1, J = 25.5 Hz, H–C–P), 7.5–6.5 (m, 9, ArH + NH); ir (Nujol) 3230 (N–H) and 1230 cm^{-1} (P=O).

Anal. Calcd for $C_{17}H_{20}NO_3P$: C, 64.35; H, 6.31; N, 4.42; P, 9.78. Found: C, 63.95; H, 6.46; N, 4.51; P, 9.79.

Diethyl 10-Acetyl-9,10-dihydroacridine-9-phosphonate.—Diethyl 9,10-dihydroacridine-9-phosphonate (**14**, 2 g) was dissolved in acetic anhydride (5 ml), treated with sulfuric acid (1 drop), and warmed on a steam bath for 30 min. The mixture was immediately poured into warm water and extracted with chloroform. Evaporation of the chloroform and crystallization from benzene–hexane gave diethyl 10-acetyl-9,10-dihydroacridine-9-phosphonate, mp 157–158°.

Anal. Calcd for $C_{19}H_{22}NO_4P$: C, 63.51; H, 6.13; N, 3.90; P, 8.64. Found: C, 63.25; H, 6.17; N, 3.70; P, 8.48.

Diisopropyl 10-Methyl-9,10-dihydroacridine-9-phosphonate (12).—Diisopropyl sodiophosphonate (18.8 g, 0.1 mol) was allowed to react with N-methylacridinium methosulfate (30.5 g, 0.1 mol) using the method described above. Crystallization of the product from benzene–hexane gave diisopropyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**12**): yield 14.4 g (40%); mp 124–125.5°; nmr ($CDCl_3$) δ 1.04 (t, 12, J = 6.5 Hz, CH_3–CH–), 3.26 (s, 3, N–CH_3), 4.24 (m, 2, J = 6.5 Hz, CH_3CHO), 4.24 (d, 1, J = 26 Hz, H–C–P), 6.65–7.35 (m, 8, ArH).

Anal. Calcd for $C_{20}H_{26}NO_3P$: C, 66.85; H, 7.24; N, 3.90; P, 8.64. Found: C, 67.28; H, 7.24; N, 3.86; P, 8.39.

9-Benzylidene-10-methyl-9,10-dihydroacridine (15).—To a solution of diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**10**, 3.3 g, 0.01 mol) and benzaldehyde (1.1 g, 0.01 mol) in 1,2-dimethoxyethane (30 ml) was added 50% sodium hydride (0.5 g, 0.01 mol). The reaction mixture was maintained at 70–75° for 40 min, poured into ice–water, and extracted with benzene. Crystallization of the residue from the benzene evaporation yielded 9-benzylidene-10-methyl-9,10-dihydroacridine (**15**): yield 2 g (70%); mp 148–149° (lit.[11] mp 143°); nmr ($CDCl_3$) δ 3.34 (s, 3, N–CH_3), 6.70 (s, 1, HC=C), 6.80–8.0 (m, 13, Ar-H).

Anal. Calcd for $C_{21}H_{17}N$; C, 89.04; H, 6.00; N, 4.95. Found: C, 89.27; H, 6.17; N, 4.80.

A sample of this compound prepared from N-methylacridone and benzylmagnesium bromide according to the method of Decker and Pschorr[11] was identical in all respects with that prepared above.

9-(*m*-Nitro)benzylidene-10-methyl-9,10-dihydroacridine (16).—*m*-Nitrobenzaldehyde was treated with phosphonate **10** in the manner used for benzaldehyde. The 9-(*m*-nitro)benzylidene-10-methyl-9,10-dihydroacridine (**17**) was obtained in 40% yield after crystallization from benzene–methanol: mp 182–185°; nmr ($CDCl_3$) δ 3.57 (s, 3, N–CH_3), 6.6–8.3 (m, 15, C=CH, ArH + 0.33C_6H_6).

Anal. Calcd for $C_{21}H_{16}N_2O_2 \cdot 0.33C_6H_6$: C, 77.97; H, 5.08; N, 7.91. Found: C, 78.01; H, 5.30; N, 7.86.

9-(*p*-Methoxy)benzylidene-10-methyl-9,10-dihydroacridine (17) was prepared from *p*-methoxybenzaldehyde and phosphonate

(18) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 220–221.

(19) W. J. Middleton, U.S. Patent 3,067,233 (1962).

(20) J. Preston and H. G. Clark, U. S. Patent 2,928,859 (1960).

10 by the procedure above. Crystallization from benzene–methanol gave an analytically pure sample in 50% yield: mp 155–156°; nmr ($CDCl_3$) δ 3.44 (s, 3, N–CH_3), 3.78 (s, 3, O–CH_3), 7.0–8.0 (m, 15, C=CH, ArH + 0.33C_6H_6).

Anal. Calcd for $C_{22}H_{19}NO \cdot 0.33C_6H_6$: C, 84.96; H, 6.19; N, 4.13. Found: C, 85.09; H, 6.38; N, 4.17.

Diethyl 9,10-Dimethyl-9,10-dihydroacridine-9-phosphonate (18).—To phosphonate **10** (3.3 g, 0.01 mol) in 1,2-dimethoxyethane (50 ml) was added a 1.6 *M* solution of butyllithium in hexane (6.5 ml, 0.01 mol) under an argon blanket. To the resulting deep red solution was added methyl iodide (2.28 g, 0.016 mol), and the reaction mixture was heated at 60° for 20 min. After cooling to room temperature, the mixture was poured into water. Extraction with benzene and crystallization from benzene–hexane gave diethyl 9,10-dimethyl-9,10-dihydroacridine-9-phosphonate (**18**): yield 1.7 g (50%); mp 112–113.5°; nmr ($CDCl_3$) δ 1.10 (t, 6, J = 7 Hz, CH_3CH_2O), 2.96 (d, 3, J = 15 Hz, CH_3CP), 3.24 (s, 3, N–CH_3), 3.68 (m, 4, J = 7 Hz, CH_3CH_2O) 6.7–7.5 (m, 8, ArH).

Anal. Calcd for $C_{19}H_{24}NO_3P$: C, 66.09; H, 6.96; N, 4.06; P, 8.99. Found: C, 66.08; H, 6.90; N, 3.95; P, 8.94.

Methylation of Diethyl 9,10-Dihydroacridine-9-phosphonate (14).—Diethyl 9,10-dihydroacridine-9-phosphonate (**14**) (6.34 g, 0.02 mol) suspended in 1,2-dimethoxyethane (50 ml) was treated with a 1.6 *M* solution of butyllithium in hexane (12.5 ml, 0.02 mol). To the resultant red solution methyl iodide (2.8 g, 0.02 mol) was added dropwise. After stirring at ambient temperature for 30 min, water (50 ml) was added, the organic layer was separated, and the aqueous portion was extracted with benzene. Evaporation of the combined organic fractions and crystallization from benzene–hexane gave unreacted starting material, yield 2.1 g (33%), mp 186–188°. The mother liquors were concentrated and chromatographed on alumina from benzene. Elution with chloroform, concentration, and crystallization from benzene–hexane yielded diethyl 9,10-dimethyl-9,10-dihydroacridine-9-phosphonate (**18**, 2 g, 30%, mp 110–111°), identical with the sample prepared above. No monoalkylated products were isolated although tlc suggested the presence of other products in the reaction.

Benzylation of Diethyl 9,10-Dihydroacridine-9-phosphonate (14).—To a stirred suspension of phosphonate **14** (6.34 g, 0.02 mol) in 1,2-dimethoxyethane (100 ml) was added a 1.6 *M* solution of butyllithium in hexane (25 ml, 0.04 mol) with cooling to keep the temperature below 10°. To the resulting lithio derivative was added benzyl bromide (7.7 g, 0.045 mol) in dimethoxyethane (10 ml) at 10°. After stirring 2 hr at 10–20° the mixture was poured into water (200 ml). Extraction with benzene and crystallization from benzene–hexane gave diethyl 9-benzyl-9,10-dihydroacridine-9-phosphonate (**20**): yield 3.9 g (47%); mp 201–204°; nmr ($CDCl_3$) δ 1.16 (t, 6, J = 7 Hz, CH_3CH_2O), 4.84 (m, 4, J = 7 Hz, CH_3CH_2O), 4.96 (d, 2, J = 8 Hz, $PhCH_2$–CP), 6.5–8.0 (m, 16, ArH + NH + 0.33C_6H_6); ir (Nujol) 3200 (N–H) and 1200 cm^{-1} (P=O).

Anal. Calcd for $C_{24}H_{26}NO_3P \cdot 0.33C_6H_6$: C, 72.06; H, 6.47; N, 3.23; P, 7.16. Found: C, 72.06; H, 6.67; N, 3.29; P, 7.31.

Crystallization of the mother liquors from monobenzyl compound **20** gave (benzene–hexane) diethyl 9,10-dibenzyl-9,10-dihydroacridine-9-phosphonate (**19**): yield 2 g (20%); mp 172–174°; nmr ($CDCl_3$) δ 1.15 (t, 6, J = 7 Hz, CH_3CH_2O), 3.9 (m, 6, CH_3CH_2O + $PhCH_2N$), 5.03 (s, 2, $PhCH_2CP$), 6.5–8.0 (m, 18, ArH).

Anal. Calcd for $C_{31}H_{32}NO_3P$: C, 74.85; H, 6.44; N, 2.82; P, 6.24. Found: C, 74.49; H, 6.54; N, 2.73; P, 6.39.

Diethyl Acridine-9-phosphonate (22).—Diethyl 9,10-dihydroacridine-9-phosphonate (**14**) (2 g, 0.0095 mol) and tetrachlorobenzoquinone (2.5 g, 0.0095 mol) were heated under reflux in benzene (50 ml) for 1 hr. The solid which separated on cooling was filtered off and discarded (tetrachlorohydroquinone). The benzene solution was concentrated to 25 ml and chromatographed on alumina. Elution with chloroform and evaporation yielded a yellow solid. Crystallization from benzene–hexane gave diethyl acridine-9-phosphonate (**22**): yield 2 g (66%); mp 95–96°; nmr ($CDCl_3$) δ 1.23 (t, 6, J = 7 Hz, CH_3CH_2O), 4.25 (m, 4, J = 7 Hz, CH_3CH_2O), 7.74 (m, 4, H at $C_{2,3,6,7}$), 8.30 (m, 2, H at $C_{4,5}$), 9.35 (m, 2, H at $C_{1,8}$); uv max (MeOH) 369 mμ (log ϵ 4.06), 255 (4.20), and 210 (4.18).

Anal. Calcd for $C_{17}H_{18}NO_3P$: C, 64.76; H, 5.71; N, 4.44; P, 9.84. Found: C, 64.64; H, 5.78; N, 4.20; P, 9.56.

Acridine-9-phosphonic Acid (23).—Diethyl acridine-9-phosphonate (**22**, 750 mg) was heated under reflux with 18% hydrochloric acid (25 ml) for 3 hr. After 2 hr an orange-yellow solid began to separate. After cooling the solid was filtered, washed with water, and dried. The acid was purified by dissolving in 3 *N* sodium hydroxide and precipitation with hydrochloric acid. The precipitate of acridine-9-phosphonic acid (**23**) was filtered, washed with water, and dried: mp >300°; ir (Nujol) 1165 cm^{-1} (P=O).

Anal. Calcd for $C_{13}H_{10}NO_3P \cdot 2H_2O$: C, 52.88; H, 3.39; N, 4.76; P, 10.51; H_2O, 12.2. Found: N, 4.85; P, 10.84; H_2O, 10.9.

Ethyl Hydrogen 9-Ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (28).—To a solution of diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**10**, 16.6 g, 0.05 mol) in dry benzene (200 ml) was added a 3 *M* solution of methylmagnesium chloride in tetrahydrofuran (51 ml, 0.15 mol) during 20 min. After stirring at room temperature for 2 hr dilute hydrochloric acid was added to the reaction. The organic phase was separated and the aqueous portion was extracted with chloroform. Evaporation of the combined organic layers and crystallization from ethanol gave ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (**28**): yield 11 g (80%); mp 217–219° dec; nmr ($CDCl_3$) δ 0.74 (t, 3, J = 7 Hz, CH_3CH_2C), 0.93 (t, 3, J = 7 Hz, CH_3CH_2O), 2.48 (q, 2, J = 7 Hz, CH_3CH_2C), 3.30 (s, 3, N–CH_3), 3.57 (q, 2, J = 7 Hz, CH_3CH_2O), 6.7–7.8 (m, 8, ArH), 11.50 (s, 1, O–H).

Anal. Calcd for $C_{18}H_{22}NO_3P$: C, 65.26; H, 6.65; N, 4.23; P, 9.37; equiv wt, 331.4. Found: C, 65.34; H, 7.02; N, 4.19; P, 9.56; equiv wt, 329 (KOH titration).

Diethyl 9-Ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (21).—Ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (**28**, 2 g) was heated at 140–150° with triethyl orthoformate (3 ml) for 20 hr. The solid phosphonate (**28**) gradually dissolved as reaction proceeded. Upon cooling crystals separated which were filtered and recrystallized from benzene–hexane to yield analytically pure diethyl 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (**21**): yield 1.8 g (82%); mp 112–113°; nmr ($CDCl_3$) δ 0.78 (t, 3, J = 7 Hz. CH_3CH_2C), 1.08 (t, 6, J = 7 Hz, CH_3CH_2O), 2.67 (q, 2, J = 7 Hz, CH_3–CH_2C), 3.37 (s, 3, N–CH_3), 3.77 (q, 4, J = 7 Hz, CH_3CH_2O), 6.8–7.6 (m, 8, ArH).

Anal. Calcd for $C_{20}H_{26}NO_3P$: C, 66.85; H, 7.24; N, 3.90; P, 8.64. Found: C, 66.94; H, 7.29; N, 4.13; P, 8.64.

Tetraethyl 9,10-Dihydroacridine-9,9-diphosphonate (24).—Diethyl sodiophosphonate (4 g, 0.025 mol) in dioxane (20 ml) was added during 20 min to 9-chloroacridine (5 g, 0.023 mol) in dimethylformamide (45 ml). The temperature of the reaction mixture rose to 55° during the addition. After stirring overnight at ambient temperature, the mixture was poured into water (200 ml) and the solid which precipitated was filtered and dried (3 g, 51%). Recrystallization from benzene–hexane gave tetraethyl 9,10-dihydroacridine-9,10-diphosphonate (**24**): yield 2 g (34%); mp 211–213°; nmr ($CDCl_3$) δ 1.07 (t, 12, J = 7 Hz, CH_3CH_2O), 4.10 (q, 8, J = 7 Hz, CH_3CH_2O), 7.05–6.55 (m, 6, H at $C_{1,2,3,6,7,8}$), 7.70 (s, 1, N–H), 8.06 (m, 2, H at $C_{4,5}$); uv max (MeOH) 332 mμ (log ϵ 3.94), 292 (4.11), 282 (4.13), and 209 (4.61); ir (Nujol) 3300 (N–H), 1240 (P=O), 1225 (P=O), 1040 cm^{-1} (P–O–C); ir (benzene) 3460 (N–H), 1250 cm^{-1} (P=O).

Anal. Calcd for $C_{21}H_{29}NO_6P_2$: C, 55.63; H, 6.48; N, 3.09; P, 13.69. Found: C, 56.09; H, 6.46; N, 3.0; P, 13.52.

Reaction of Diethyl Acridine-9-phosphonate (22) with Diethyl Sodiophosphonate.—Sodium (0.1 g) was added to diethyl phosphite (2 g) in dimethylformamide (5 ml) to give diethyl sodiophosphonate. To this reagent was added diethyl acridine-9-phosphonate (1.3 g) and the mixture was heated at 50–55° for 30 min. After cooling, the reaction mixture was poured into water and the precipitated solid was filtered and dried. Crystallization of the solid from benzene–hexane gave tetraethyl 9,10-dihydroacridine-9,9-diphosphonate (**24**), yield 1.4 g (65%), mp 211–213°. This compound gave identical spectral data as the sample from 9-chloroacridine.

Tetraethyl 10-Acetyl-9,10-dihydroacridine-9,10-diphosphonate (25).—Tetraethyl 9,10-dihydroacridine-9,10-diphosphonate (**24**) (500 mg) was heated at 80° for 10 min in acetic anhydride (5 ml) containing 1 drop of sulfuric acid. The crude acetyl derivative was obtained by pouring the reaction mixture into warm water and extraction with ether. The ether extract was evaporated and the residue crystallized from benzene–hexane to yield tetraethyl 10-acetyl-9,10-dihydroacridine-9,10-diphosphonate (**25**), yield 400 mg, mp 120–122°.

Anal. Calcd for $C_{23}H_{31}NO_7P_2$: C, 55.76; H, 6.26; N, 2.83; P, 12.53. Found: C, 56.45; H, 6.39; N, 2.80; P, 12.40.

Registry No.—**10**, 19656-30-5; **12**, 19656-31-6; **14**, 19656-32-7; **15**, 19656-33-8; **16**, 19656-34-9; **17**, 19656-35-0; **18**, 19656-36-1; **19**, 19656-37-2; **20**, 19656-38-3; **21**, 19656-39-4; **22**, 19656-40-7; **23**, 19656-41-8; **24**, 19656-42-9; **25**, 19656-43-0; **28**, 19656-44-1; diethyl 10-acetyl-9,10-dihydroacridine-9-phosphonate, 19656-45-2.

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Dual Formation of β Diketones from Methylene Ketones and Acetic Anhydride by Means of Boron Trifluoride. Improved Method of Synthesis of Certain β Diketones[1]

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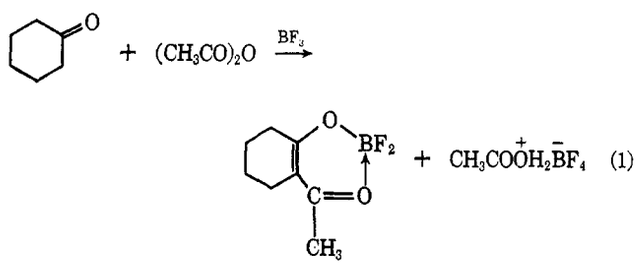
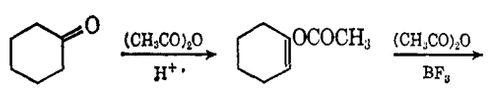
Evidence is presented that the formation of β diketones from methylene ketones and acetic anhydride by means of boron trifluoride involves, not only direct C acetylation of the ketone, but also O acetylation of the ketone and C acetylation of the resulting ketone enol ester. The O acetylation is catalyzed by proton acid formed as the by-product in the C acetylation of the ketone. Certain intermediate ketone enol esters, β diketone enol esters, and boron difluoride complexes were isolated. Acetophenone, however, apparently undergoes only C acetylation. The relative proportions of the methyl and methylene derivatives of methyl methylene ketones were found to be dependent, not only on the structure of the ketone, but also on the conditions employed for effecting the acetylation. Several β diketones were prepared conveniently by use of the boron trifluoride–diacetic acid complex which is available commercially.

In 1954,[2] the acylation of a ketone with an aliphatic anhydride by boron trifluoride to form a β diketone was suggested to involve, not only C acylation of the ketone, but also O acylation of the ketone followed by C acylation of the resulting ketone enol ester.

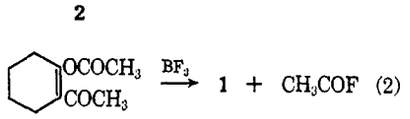
We now present evidence for such dual formation of β diketones from certain methylene ketones and acetic anhydride. Thus cyclohexanone and this anhydride were found to be converted by boron trifluoride into boron difluoride complex **1**, not only by direct C acetylation of the ketone (eq 1), but also indirectly through ketone enol acetate **2** and β diketone enol acetate **3** (eq 2). Although the second course of reaction is dependent on formation of proton acid as by-product in the first course (see eq 1 and 2), the O acetylation may be initiated soon after the boron trifluoride is added, since only a catalytic amount of the proton acid is required. The boron difluoride complex **1** was subsequently treated with hot sodium acetate solution to liberate the β diketone.



1



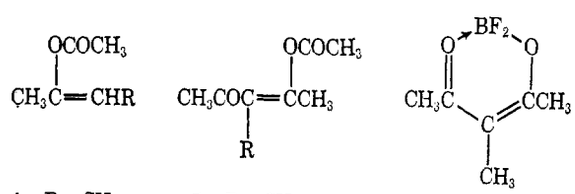
2



3

In support of the O acetylation course of reaction (eq 2), the intermediate ketone enol acetate **2** and the β diketone enol acetate **3** were isolated from the reaction mixture of cyclohexanone and acetic anhydride and subsequently converted into the boron difluoride complex **1** or 2-acetylcyclohexanone under similar conditions. In the further reaction of the β diketone enol acetate **3**, acetyl fluoride was shown to be formed as by-product (see eq 2).

Similarly, ketone enol acetates **4a** and **b** and β diketone enol acetates **5a** and **b** were isolated from the reaction mixtures of the appropriate ketones, acetic anhydride and boron trifluoride, and certain of them were subsequently converted into β diketones or their boron difluoride complexes such as **6**. Previously, certain ketone enol esters and β diketone enol esters have been converted into β diketones or their difluoride complexes; benzoyl fluoride was shown to be eliminated from a β diketone enol benzoate.[3]



4a, R = CH_3; **b**, R = n-C_4H_9 **5a**, R = CH_3; **b**, R = n-C_4H_9 **6**

(1) Supported by the National Science Foundation.

(2) *Org. Reactions*, **8**, 98 (1954).

(3) See C. R. Hauser, F. C. Frostick, Jr., and E. H. Man, *J. Amer. Chem. Soc.*, **74**, 3231 (1952).