2.4 g of acetic acid was treated as described in the last experiment up to the point of drying the reaction mixture over calcium chloride. The dried solution was evaporated to give 2.2 g of a viscous residue, whose ir spectrum showed that it consisted of unreacted α-(9-acridanyl)propionitrile and some unknown carbonyl-containing materials.

The acidic aqueous extracts and washings from above were treated with aqueous ammonia to liberate the free base which was filtered, washed with water, and dried to give 3.0 g of a mixture of two compounds, mp 50–90°. Repeated crystallization of this mixture from ether–petroleum ether gave 1.9 g (41%) of α-(9-acridinyl)propionitrile (A), mp 115.5–117° (yellow crystals from heptane containing a small amount of pyridine), and 0.4 g (8.5%) of α-cyano-α-methyl-9-methyleneacridan (B), mp 197–199° from ether–petroleum ether.

Anal. of A. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.81; H, 5.39; N, 12.38. *Anal.* of B. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06 Found: C, 82.35; H, 5.18; N, 11.97.

The ir spectrum of A showed a weak C≡N band at 4.43 μ and a strong aromatic band at 13.27 μ. There were no N–H bands present and there was no absorption in the 6.0–6.2-μ region. The ir spectrum of α-cyano-α-methyl-9-methyleneacridan (B) showed an N–H band at 2.96 μ, a strong C≡N band at 4.52 μ, a strong, sharp band at 6.20 μ (indicative of a conjugated double bond), and various aromatic bands.

Heating A briefly above its melting point converted it quantitatively to B. This conversion also occurred when A was kept at room temperature for 6 months. These conversions were verified from their ir spectra and melting points.

3. Dehydrogenation of α-(9-Acridanyl)phenylacetonitrile. Lead tetraacetate (8.8 g, 0.02 mol) containing acetic acid (2.6 ml) was added slowly at room temperature to a stirred solution of α-(9-acridanyl)phenylacetonitrile (5.9 g, 0.02 mol) in 300 ml of benzene. After stirring at room temperature for 1 hr, the lead salts were filtered and the benzene filtrate was washed with four 100-ml portions of water and was dried over calcium chloride. The benzene solution was concentrated to 80 ml and was diluted with 250 ml of ether. The resulting solution was extracted with three 100-ml portions of 6 *N* hydrochloric acid and was then washed with four 100-ml portions of water. After drying over calcium chloride, the solvents were evaporated to give 3.2 g of a residue, mp 45–200°; its ir spectrum showed that it contained unreacted α-(9-acridanyl)phenylacetonitrile and some unknown materials containing carbonyl functions which were not characterized further.

The combined acidic aqueous extracts and washings from above were treated with aqueous ammonia to liberate the free base which separated as an oil. This product was dissolved in ether and, after washing with water and drying (calcium chloride), the ether was evaporated to give 2.7 g of reddish, gummy solid, mp 35–55°; its ir spectrum showed an N–H band at 2.91 μ, a strong C≡N band at 4.53 μ, and various aromatic bands and agrees with the structure of α-cyano-α-phenyl-9-methyleneacridan. The very crude product was repeatedly recrystallized from benzene–petroleum ether to give 0.5 g (7.5%) of pure α-cyano-α-phenyl-9-methyleneacridan, mp 209.5–210.5° [literature value for α-(9-acridinyl)-α-phenylacetonitrile, 210°[4]].

Anal. Calcd for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79. Found: C, 85.65; H, 5.08.

Its ir spectrum was identical with that described above.

The dehydrogenation of α-(9-acridanyl)propionitrile gave a mixture of two products. (a) α-Cyano-α-methyl-9-methyleneacridan (8.5%, mp 197–199° from ether–petroleum ether). *Anal.* Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.35; H, 5.18; N, 11.97. (b) α-(9-Acridinyl)propionitrile (41% 115.5–117° from heptane). *Anal.* Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.81; H, 63.9; N, 12.58.

Registry No.—**2** (R = R′ = H, 22409-47-8; **2** (R = H; R′ = C_6H_5), 52673-98-0; **2** (R = H; R′ = CH_5) 1:1 adduct with acridine, 52673-99-1; **2** (R = H; R′ = CH_3), 52674-00-7; **3** (R = H; R′ = CH_3), 52674-01-8; **4**, 52674-02-9; **5**, 52674-03-0; **6**, 52674-04-1; **7**, 52674-05-2; acridine, 260-94-6; acetonitrile, 75-05-8; phenylacetonitrile, 140-29-4; propionitrile, 107-12-0; isobutyronitrile, 78-82-0.

References and Notes

(1) F. Kröhnke and H. L. Honig, *Ann.*, **624**, 97 (1959).
(2) C. S. Sheppard and R. Levine, *J. Heterocycl. Chem.*, **1**, 61 (1964).
(3) R. M. Acheson and L. E. Orgel, "Acridines," Interscience Publishers, New York, N.Y., 1956.
(4) H. Lettré, P. Jungman, and J. Salfield, *Chem. Ber.*, **85**, 397 (1952).
(5) Y. Mizuno, K. Adachi, and K. Ikedo, *Pharm. Bull. Jap.*, **2**, 225 (1954); *Chem. Abstr.*, **50**, 1035 (1956).
(6) We thank one of the referees for pointing out these spectral correlations and suggesting the importance of structure **9**. For a complete discussion of the ir spectra of the acridines and acridans see "Acridines," R. M. Acheson, Ed., 2nd ed., Interscience, New York, N.Y., 1973, Chapter 11, pp 665–685.

Certain Condensations Effected by 2,6-Dimethoxyphenyllithium

Robert Levine* and Jay R. Sommers

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received May 30, 1974

2,6-Dimethoxyphenyllithium (2,6-DMPL) can be acylated with several aromatic and heterocyclic esters to give ketones. The use of methyl isonicotinate gave 2,6,2′,6′-tetramethoxydiphenylcarbinol and no ketone. Methyl anisate and 2,6-DMPL gave a mixture of 2,6,4′-trimethoxybenzophenone and 4-(2,6,2′,6′-tetramethoxydiphenylmethylene)-2,5-cyclohexadienone. Several aliphatic esters were used to give ketones, carbinols, or a mixture of the two. With the three esters, ethyl acetate, ethyl propionate, and ethyl phenylacetate, which contain α-hydrogen atoms, small amounts of β-keto esters (for the first two esters) or the ketonic cleavage product of the β-keto ester (for the third ester) were formed. While 2-picoline, 4-picoline, and methylpyrazine can be benzoylated using 2,6-DMPL at their methyl groups with methyl benzoate, this reaction fails with 3-picoline and 2,6-dimethoxybenzophenone is formed.

Resorcinol dimethyl (RDME) was first metalated by Wittig and Pockels[1] by reaction with phenyllithium at room temperature for 60 hr to give 2,6-dimethoxyphenyllithium (2,6-DMPL) which was treated with gaseous carbon dioxide to give a mixture of 2,6,2′,6′-tetramethoxybenzophenone (25%) and 2,6-dimethoxybenzoic acid (20%). Several other condensations have been effected with 2,6-DMPL including its reaction (1) with *N*-methylformanilide[2] to give 2,6-dimethoxybenzaldehyde (55%); (2) with benzophenone[3] to give 2,6-dimethoxydiphenylcarbinol; (3) with a series of α,ω-dibromoalkanes to give α,ω-bis(2,6-dimethoxyphenyl)alkanes[4] (50–90%); (4) with aliphatic and aromatic nitro compounds[5] to give a series of nitroxides; and (5) with the sterically hindered ketone 2,6,2′,6′-tetramethoxybenzophenone[6] to give 2,6,2′,6′,2″,6″-hexamethoxytriphenylcarbinol in 77.8% yield.

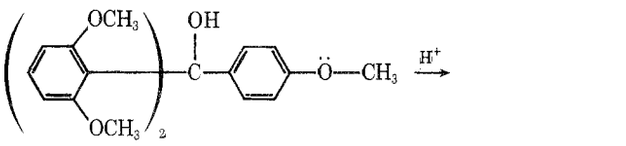
Of particular interest in connection with the present problem (*vide infra*) is the work of Limaye and cowork-

ers[7-10] who studied the reactions of coumarin derivatives as a route to 2,6-dimethoxyacylbenzenes. Their route involves a six-step synthesis starting with resorcinol.

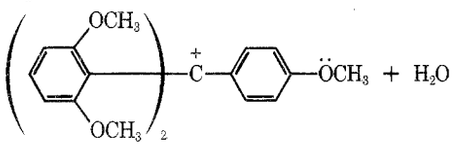
The present study was undertaken to determine whether 2,6-DMPL can be acylated with a series of aliphatic, aromatic, and heterocyclic esters to give directly sterically hindered ketones, the 2,6-dimethoxyacylbenzenes in a one-step process and to ascertain whether these reactions give any carbinols, which would also be sterically hindered. Another aim was to determine, in those cases where the acylating esters have α-hydrogen atoms, whether the esters self-condensed to an appreciable extent to give the corresponding β-keto esters. Finally, it was of interest to determine the feasibility of using 2,6-DMPL as the condensing agent in the benzoylation of certain methylated heterocyclic nitrogen compounds.

The required 2,6-DMPL was prepared in 70% yield by the interaction of equivalents of resorcinol dimethyl ether (RDME) and *n*-butyllithium in refluxing ether for 2 hr. The conversion of RDME to 2,6-DMPL was determined by carbonation and isolating the 2,6-dimethoxybenzoic acid. As an orienting experiment both commercial and freshly prepared 2,6-DMPL were acylated with methyl benzoate to give 2,6-dimethoxybenzophenone in 36.3% yield with the former and in 81.0% yield with the latter source of 2,6-DMPL. In all other experiments the 2,6-DMPL was freshly prepared prior to use. Although 2,6-dimethoxybenzophenone was prepared by Limaye's[7-10] multistage synthesis, an overall yield was not reported.

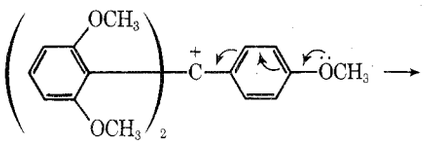
With methyl anisate there was obtained the new ketone, 2,6,4′-trimethoxybenzophenone (55.8%) as well as 17.5% yield of 4-(2,6,2′,6′-tetramethoxydiphenylmethylene)-2,5-cyclohexadieneone (**4**). This unsaturated ketone appears to arise from the gross loss of the elements of methanol from the initially formed 2,6,2′,6′,4″-pentamethoxytriphenylcarbinol, (**1**) when the reaction mixture is processed in the presence of hydrochloric acid.



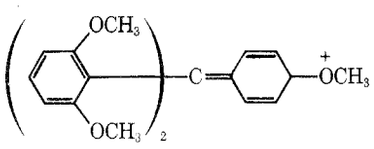
1



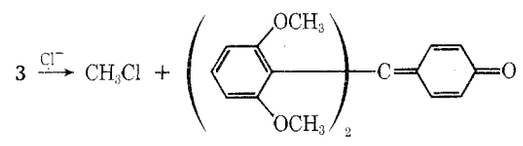
2



2

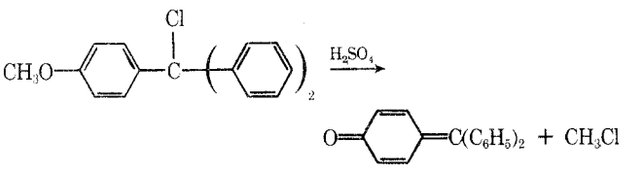


3



4

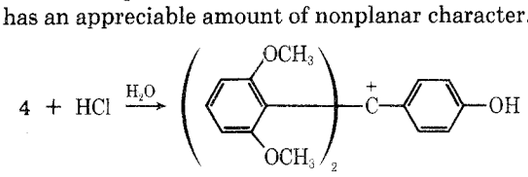
This scheme is somewhat analogous to the two mechanisms proposed by Filar and Winstein[11] for the conversion of 3,5-dimethyl-4-hydroxybenzyl chloride to 2,6-dimethyl-4-methylene-2,5-cyclohexadienone. The cleavage of the para ether function in the conversion of **1** to **4** in an acidic medium is not without precedent since it has been reported[12] that the reaction of *p*-methoxytriphenylchloromethane with sulfuric acid gives 4-diphenylmethylene-2,5-cyclohexadienone and methyl chloride.



Elemental analysis and spectral methods were used to elucidate the structure of **4.** The ir spectrum shows a carbonyl band at 1628 cm^{-1}, which indicates the presence of a quinoidal system and is in good agreement with the reported values for the carbonyl peak of 2,6-dimethyl-4-methylene-2,5-cyclohexadienone (1625 cm^{-1})[11] and other quinoidal systems (1605 cm^{-1}).[13]

The nmr spectrum integrates correctly for the indicated structure. There is a doublet at τ 3.75 (2 H) which is assigned to the protons ortho to the disubstituted 4-methylene group. This value agrees with the reported average values for a proton bonded to a quinone ring.[14]

Martin and Smith[15] have found that when 2,6,2′,6′,2″,6″-hexamethoxytriphenylcarbinol is dissolved in dilute hydrochloric acid, a purple color arises due to the formation of the 2,6,2′,6′,2″,6″-hexamethoxytriphenylmethyl carbonium ion, which they propose exists to an appreciable extent in a highly nonplanar or an exaggerated "propeller" conformation. Similarly, we have found that when **4** is dissolved in 6*N* hydrochloric acid a purple color is formed probably by the formation of the carbonium ion **5,** which is the protonated form of **4** and which also probably has an appreciable amount of nonplanar character.



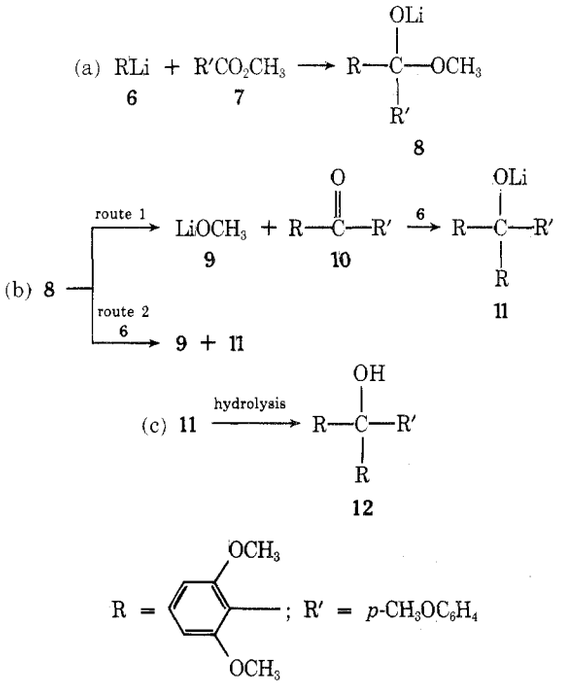
The cyclohexadienone, **4,** gives a λ_{max} at 510 mμ in 6 *M* hydrochloric acid and its calculated λ_{max} using 4-diphenylmethylene-2,5-cyclohexadienone as the parent chromophore (λ_{max} 470 mμ in 100% hydrochloric acid)[16] and allowing 7 mμ for each *o*-methoxy group[17] is 498 mμ (Δmμ = −12). Although this calculation is in reasonably good agreement with the observed data, the steric contribution of the methoxy groups has not been taken into consideration.

Triphenylcarbinol has a λ_{max} at 435 mμ in sulfuric acid,[18] while the carbonium ion derived from 2,6,2′,6′,2″6″-hexamethoxytriphenylcarbinol in 0.5 *M* hydrochloric acid has a λ_{max} at 522 mμ.[15] This represents a difference of 87 mμ or a contribution of 14.5 mμ for each *o*-methoxy group including steric hindrance. Therefore, the four methoxy groups in **5** (the carbonium ion derived by protonating **4**) add 58 mμ to the λ_{max} of the parent chromophore to give a calculated λ_{max} of 528 (Δmμ = +18). From these calculations it is concluded that there is some steric contribution from the four *o*-methoxy groups in **5** but it is not as great as the steric contribution of the six *o*-methoxy groups in the carbonium ion derived from 2,6,2′,6′,2″,6″-hexamethoxytriphenylcarbinol.

It has been reported that the effect of twisting the aryl groups out of the central plane of the carbonium ion by the

o-methoxy groups is a shift to longer wavelengths with the accompanying lowering of the extinction coefficient.[19] This trend can be seen in the two quinoidal compounds: 4-diphenylmethylene-2,5-cyclohexadienone (λ_{max} 472 mμ, log ε 5.03) and 4-(2,6,2′,6′-tetramethoxydiphenylmethylene)-2,5-cyclohexadienone (λ_{max} 510 mμ, log ε 4.11).

The carbinol, **1**, which is the proposed precursor of **4** may be envisioned as arising by two paths.

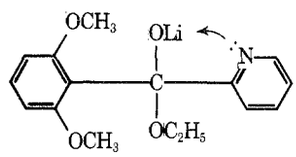


Initially (equation a), **6** adds to the carbonyl group of **7** to give the hemiacetal type of adduct, **8**, which may react further with more **6** *via* two paths: route 1, which involves the intermediacy of the ketone, **10**, and/or route 2, in which the attack by **6** on the hemiacetal like carbon atom of **8** is accompanied by the displacement of methoxide ion. Both routes give **11**, which on hydrolysis gives the carbinol, **12**.

Martin and Smith[15] found that 2,6-DMPL *does not add* to the carbonyl group of the sterically hindered ketone, 2,6,2′,6′-tetramethoxybenzophenone using ether or tetrahydrofuran as the reaction medium and that a large amount of benzene and a 3-day reaction period were required to give 2,6,2′,6′,2″,6″-hexamethoxytriphenylcarbinol in high yield, 77.8%. Therefore, two experiments were performed to determine, if possible, the course of the reaction which would lead to **12**. First the ketone, **10**, was added to **6** in *refluxing ether*. After processing the reaction mixture in the usual manner, only the starting materials were isolated. In the second experiment, the ketone, **10** (dissolved in a small amount of benzene), was added to **6** and the reaction was allowed to proceed in the usual manner, *i.e.*, the mixture was refluxed for 5 hr. Again, none of the carbinol, **12**, was obtained and only resorcinol dimethyl ether (**6**, Li replaced by H) and **10** were isolated. It should be noted that these reaction conditions are considerably milder than those used by Martin and Smith in their experiment (*vide supra*). Thus, since the dienone, **4**, is believed to arise *via* the intermediate formation of carbinol, **12**, in refluxing ether, the carbinol is most likely formed by route 2.

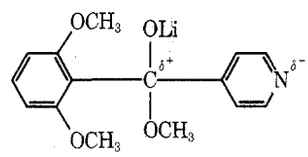
A possible explanation for the formation of **11**, the initial precursor of **4**, and the ketone, **10**, in the reaction of **6** and **7** (*vide supra*) is that the initial adduct, **8**, is especially reactive at its hemiacetal like carbon atom due to the presence of the *p*-OCH_3 group and hence this undergoes a nucleophilic displacement reaction at carbon with **6** to give **11**, the precursor of **4**, which is obtained in 17.5% yield, and not exclusively **10**, which arises in 55.8% yield.

From the reaction of 2,6-DMPL with ethyl picolinate and methyl nicotinate only the corresponding ketones were obtained in yield of 30.6 and 19.6%, respectively. Because of the proximity of the nitrogen atom to the lithium atom in the intermediate adduct which is formed between the ester and the 2,6-DMPL (shown below in **13** for the ethyl



picolinate case) there may be formed a coordinated species which prevents the nitrogen atom from creating a sufficiently reactive center at the hemiacetal like carbon atom for reaction (*vide infra* for the reaction with methyl isonicotinate) with additional 2,6-DMPL and may also prevent the reaction from proceeding further because of steric reasons.

Note that in **13** a five-membered coordinated species is postulated, while in the case of methyl nicotinate a six-membered ring might be formed. By contrast with these reactions, in the reaction of 2,6-DMPL and methyl isonicotinate only the carbinol, 2,6,2′,6′-tetramethoxydiphenyl-4-pyridylcarbinol (36.8%), was formed and no ketone was isolated. It is suggested that the initial intermediate formed in this reaction, **14**, is more reactive toward nucleophilic at-



tack by 2,6-DMPL than in the isomeric pyridine carboxylates. The nitrogen atom is withdrawing electrons from both the pyridine ring and the adjacent carbon atom by resonance and inductive effects thus generating a partial positive charge on the hemiacetal like carbon atom so that further attack can occur at this sight by 2,6-DMPL.

Several aliphatic esters were then treated with 2,6-DMPL. When a basic condensing agent, **15**, reacts with an ester possessing α-hydrogen atoms, **16**, three reactions can conceivably take place. Carbonyl attack can occur to give the adduct, **17**. Loss of MOR′ will give **18**, which is an ester (B = OC_2H_5), an amide (B = NH_2) or a ketone [B =

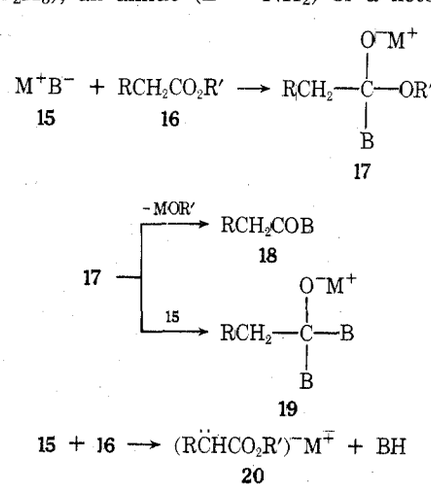
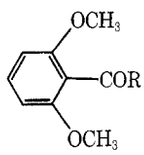
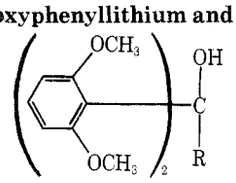


Table I
Ketones (A) and Carbinols (B) from 2,6-Dimethoxyphenyllithium and Esters



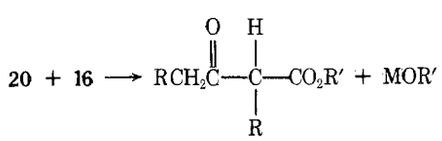
IA



IIB

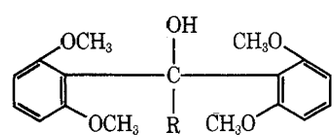
Ketone (I)				Carbinol (II)			
R	Yield, %	Registry no.	Mp or bp (°C, mm)	R	Yield, %	Registry no.	Mp, °C
C_6H_5	81	25855-75-8	98.3–99.0[a]	C_6H_5	0		
p-$CH_3OC_6H_4$[b]	55.8	52856-15-2	109.1–109.6	p-$CH_3OC_6H_4$	0		
2-C_5H_4N[c]	30.6	52856-16-3	138.4–139.0[d]	2-C_5H_4N	0		
3-C_5H_4N[e]	19.6	52856-17-4	108.8–110.0[f]	3-C_5H_4N	0		
4-C_5H_4N[g]	0			4-C_5H_4N	36.8	52856-21-0	184.0–185.4 dec
CH_3[h]	60.3	2040-04-2	71.0–72.0[i]	CH_3	0		
C_2H_5[j]	0			C_2H_5[k]	35.0	52856-22-1	120.0–120.8
n-C_3H_7	0			n-C_3H_7[l]	30.6	52856-23-2	143.7–144.1
i-C_3H_7	46.5	52856-18-5	38.9–39.2[m]	i-C_3H_7	0		
C_6H_5-CH_2[n]	26.2	52856-19-6	78.2–79.2[o]	$C_6H_5CH_2$	0		
$(CH_3)_2CHCH_2$	42.0	52856-20-9	116 (0.5)[p]	$(CH_3)_2CHCH_2$	10.4	52856-24-3	121.0–121.8[q]

[a] See ref 7. [b] 4-(2,6,2′,6′-Tetramethoxydiphenylmethylene)-2,5-cyclohexadienone (17.5%, mp 216.0–216.5° from ethanol) was also obtained. [c] 2-C_5H_4N = 2-pyridyl radical. [d] *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39. Found: C, 68.91; H, 5.60. Picrate, mp 145.0–147.8°. *Anal.* Calcd for $C_{20}H_{16}N_4O_{10}$: C, 50.85; H, 3.41. Found: C, 50.88, H, 3.29. [e] 3-C_5H_4N = 3-pyridyl radical. [f] *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39. Found: C, 69.02; H, 5.24. Picrate, mp 143.2–144.0°. *Anal.* Calcd for $C_{20}H_{16}N_4O_{10}$: C, 50.85; H, 3.41. Found: C, 51.03; H, 3.70. [g] 4-C_5H_4N = 4-pyridyl radical. [h] Ethyl acetoacetate (9.9%, bp 84–88° (22.0 mm); copper chelate, mp 193–194° alone and when mixed with an authentic sample) was also obtained. [i] See ref 8. [j] Ethyl α-propionylpropionate (16.4%, bp 87–89° (12 mm); see ref 26) was also obtained. [k] *Anal.* Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.73; H, 6.97. [l] *Anal.* Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.12; H, 7.32. [m] *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.51; H, 7.51. 2,4-Dinitrophenylhydrazone, mp 131.8–132.6°. *Anal.* Calcd for $C_{18}H_{20}N_4O_6$: C, 55.66; H, 5.19. Found: C, 55.88; H, 4.84. [n] Dibenzyl ketone (17.7%, mp 30.4–31.4° [27] alone and when mixed with an authentic sample). [o] *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; 6.29. Found: C, 75.20; H, 6.28. [p] *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.51; H, 7.96. 2,4-Dinitrophenylhydrazone, mp 147.2–148.0°. *Anal.* Calcd for $C_{19}H_{22}N_4O_6$: C, 56.71; H, 5.51. Found: C, 56.95; H, 5.78. [q] *Anal.* Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.88; 7.88.



21

M = Li, Na, K; B = OC_2H_5, NH_2, $(C_6H_5)_3C$
R = alkyl, aryl, heterocyclic; R′ = alkyl, aryl



22

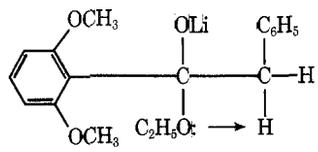
R = C_2H_5, 35.0%; n-C_3H_7, 30.6%; $(CH_3)_2CHCH_2$, 10.4%

$C(C_6H_5)_3$] or it can react with a second molecule of **15** to give the adduct **19.** While this latter reaction is uncommon when B^- = $OC_2H_5^-$, NH_2^-, or $C(C_6H_5)_3^-$ it takes place very readily when M = Li (as in organolithium compounds) or MgX (as in Grignard reagents). In addition, **15** may abstract an α proton from **16** to give the carbanion, **20,** which can react with a molecule of **16** to give β-keto ester, **21.**

Three of the esters (Table I) gave self-condensed materials as minor products when treated with 2,6-DMPL. Thus, ethyl acetate gave ethyl acetoacetate, **21** (R = H, R′ = C_2H_5) in 9.9% yield and ethyl propionate gave ethyl α-methylpropionylacetate, **21** (R = CH_3, R′ = C_2H_5). In the ethyl phenylacetate reaction there was isolated dibenzyl ketone (17.7%) which no doubt arises from the cleavage of the initially formed β-keto ester (ethyl α,γ-diphenylacetoacetate (**21,** R = C_6H_5, R′ = C_2H_5). No β-keto ester was obtained in the ethyl n-butyrate, ethyl isobutyrate, and ethyl isovalerate reactions probably for steric reasons. A comparison of these results with those obtained earlier in the self-condensation of these esters by Hammell and Levine[20] using lithium diisopropylamide as the condensing agent shows that this base is superior to 2,6-DMPL for the self-condensation of aliphatic esters.

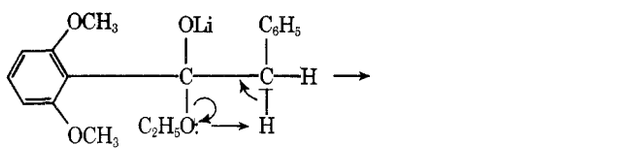
The production of carbinols, **22,** from ethyl propionate (R = C_2H_5), ethyl n-butyrate (R = n − C_3H_7), and ethyl isovalerate [R = $(CH_3)_2CHCH_2$] appears to be due to the probability that the initially formed intermediate [**17,** M = Li, R′ = C_2H_5, R = CH_3, C_2H_5, and $(CH_3)_2CH$, and B = 2,6-dimethoxyphenyl] is sufficiently reactive and insufficiently sterically hindered at its hemiacetal like carbon atom so that it reacts to some extent with a second molecule of 2,6-DMPL. It is not surprising that an increase in the size of R in **17** from CH_3 to C_2H_5 to $(CH)_2CH$ results in a decrease in carbinol formation, **22,** from 35.0 to 30.6 to 10.4%. The hemiacetal like carbon atom in the adduct which is formed in the case of ethyl isobutyrate [**17,** RCH_2 is replaced by $(CH_3)_2CH$, R′ = C_2H_5 and B = 2,6-dimethoxyphenyl] appears to be sufficiently sterically hindered so that carbinols are not formed and ketones are produced exclusively, *viz.,* 2,6-dimethoxyisobutyrophenone (46.8%) and 2,6-dimethoxypivalophenone (81.7%), respectively. In the case of ethyl isovalerate the hemiacetal like carbon atom in the intermediate adduct **17** [R = $(CH_3)_2CH$, R′ = C_2H_5, B = 2,6-dimethoxyphenyl] is moderately sterically hindered so that the major product is the ketone **18** [R = $(CH_3)_2CH$, B = 2,6-dimethoxyphenyl, 42.0%] and the minor product is the carbinol, **22** [R = $(CH_3)_2CHCH_2$, 10.4%].

That no carbinol was isolated from the ethyl phenylacetate–2,6-DMPL reaction may be interpreted as follows. The initially formed adduct between these two reagents

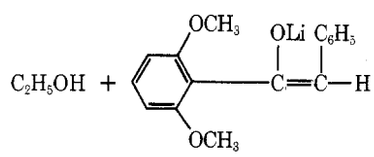


23

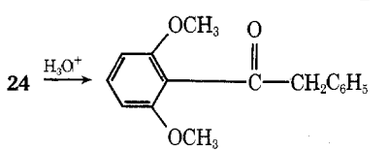
may be represented by the hydrogen bonded structure, **23.** Its benzylic hydrogen atoms appear to be sufficiently acidic so that ethanol is rapidly and completely lost to give the lithium derivative of the enol form of benzyl 2,6-dimethoxyphenyl ketone, **24,** before it can react with a second molecule of 2,6-DMPL to give the carbinol. Hydrolysis of **24** gives the ketone, **25.** A similar explanation can be used to



23



24



25

account for the fact that the reaction of 2,4-DMPL with the relatively reactive ester, ethyl acetate, gives only a ketonic product and no carbinol.

Finally, it was of interest to determine whether 2,6-DMPL with its two ortho substituents would or would not be sufficiently sterically hindered to undergo azomethine addition to certain methylated heterocyclic nitrogen compounds and also whether this lithium base could remove a lateral proton from these nitrogeneous bases.

2-Picoline was acylated with methyl benzoate to give 2-phenacylpyridine (43.7%) using 2,6-DMPL [prepared from resorcinol dimethyl ether (RDME) and *n*-butyllithium] as the condensing agent and no azomethine addition product was isolated. This yield is considerably lower than was obtained[21] using phenyllithium as the condensing agent (81.8%).

The benzoylation of 4-picoline with 2,6-DMPL (prepared from RDME and phenyllithium) gave 4-phenacylpyridine (41.8%) which is almost as high as the yield (48.4%) obtained with methyllithium[22] and was unaccompanied by azomethine addition products. However, 2,6-DMPL is more effective than phenyllithium for this reaction since the latter base gave[22] a mixture of 4-phenacylpyridine (12.1%) as well as the azomethine addition products, 2-phenyl-4-methylpyridine (39.2%) and 2,6-diphenyl-4-methylpyridine (33.3%).

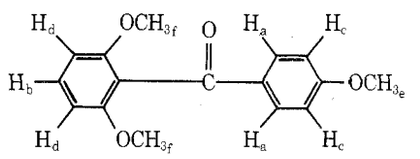
Apparently, 2,6-DMPL is not a strong enough base to remove a lateral proton from 3-picoline, since the interaction of these reagents followed by the addition of methyl benzoate gave only 2,6-dimethoxybenzophenone (40.3%) which arises from the interaction of the ester and 2,6-DMPL, and none of the acylated tar base, 3-phenacylpyridine. Again no azomethine addition products were isolated.

Finally, methylpyrazine was benzoylated in 47.0% yield using 2,6-DMPL as the condensing agent. This method is, therefore, more effective than that using phenyllithium which gave[23] a 4.0% yield of product but less effective than sodium amide which gave the phenacylpyrazine in 94.6% yield.[23]

Experimental Section

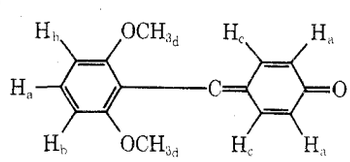
Preparation of 2,6-Dimethoxyphenyllithium (2,6-DMPL) and Its Conversion to 2,6-Dimethoxybenzoic Acid. In the standard apparatus was placed 100–200 ml of anhydrous ether and *n*-butyllithium (0.1 mol, 62.5 ml, 15 weight % in *n*-hexane, supplied through the courtesy of Dr. W. T. Barrett, Foote Mineral Co., Exton, Pa.). Then resorcinol dimethyl ether, RDME, (0.1 mol, 13.8 g, supplied through the courtesy of Koppers Co., Pittsburgh, Pa.) in an equal volume of ether was added. The mixture was refluxed for 2 hr and poured onto Dry Ice. After the excess carbon dioxide had evaporated the mixture was acidified with concentrated hydrochloric acid and filtered to give 9.0 g of a purple solid. The filtrate was extracted with several portions of ether, the combined extracts were dried (sodium sulfate), the solvent was removed at atmospheric pressure, and the residue was vacuum distilled to give 2.4 g (17.2%) of recovered RDME (bp 106–110° (24.0 mm), lit.[24] bp 212–215° (760 mm)), 4.6 g of a purple solid, and 2.4 g of a tarry residue. The combined solids had mp 170–175° crude (white crystals, mp 184.8–185.8° (12.7 g, 70.0%)) from water alone and when mixed with an authentic sample[25] of 2,6-dimethoxybenzoic acid. The yield of the 2,6-DMPL is 70.0% based on the amount of acid isolated.

Reaction of 2,6-DMPL with Methyl Anisate. 2,6-DMPL [0.035 mol, made from 0.05 mol of *n*-butyllithium (31.0 ml) and RDME (0.05 mol, 6.9 g)] and methyl anisate (0.05 mol, 8.3 g in an equal volume of ether) were refluxed in 100 ml of ether for 5 hr. The usual processing gave RDME (1.3 g, 18.9%, bp 87–93° (7.0 mm)), methyl anisate (2.4 g, 29.0%, bp 85–92° (0.8 mm)), 2,6,4′-trimethoxybenzophenone, A (5.3 g, 55.8%, bp 134–150° (0.8 mm); mp 109.1–109.6° from ethanol), and 2.3 g (17.5%) of 4-(2,6,2′,6′-tetramethoxy-diphenylmethylene)-2,5-cyclohexadienone, B (mp 216.0–216.5° from ethanol). *Anal.* of A. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.30, H, 6.11. Ir spectrum of A in carbon tetrachloride: weak C–H stretch (2940 cm^{-1}), very strong C=O stretch (1663 cm^{-1}), very strong aromatic C=C vibrations (1590 and 1471 cm^{-1}); very strong aralkyl ether (1289 and 1250 cm^{-1}) and very strong aromatic C=O (1114 cm^{-1}). Nmr spectrum of A in $CDCl_3$.



Group	τ (ppm)	Rel intensity
a	2.22	1.9
b	2.70	1.3
c	3.15	2.0
d	3.40	1.8
e	6.18	3.3
f	6.30	5.7

Anal. of B. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 72.72; H, 5.83. Ir spectrum of B in chloroform: very strong C—H stretch (3010 cm^{-1}), very strong C=O stretch (1628 cm^{-1}), very strong aromatic C=C vibrations (1585, 1515, 1468, and 1429 cm^{-1}) and very strong aralkyl ether (1282 and 1250 cm^{-1}). Nmr spectrum of B in $CDCl_3$.

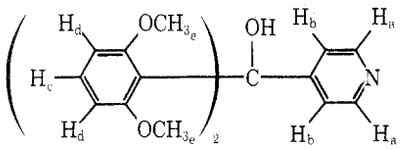


Group	τ (ppm)	Rel intensity
a	2.74	4.2
b	3.46	4.1
c	3.73	1.9 (J = 10 H_2)
d	6.38	12.0

Visible spectrum (69 mg/l.) in 6 *M* HCl: λ_{max}, 510 mμ, log ε = 4.11. Uv spectrum (69 mg/l.) in 6 *M* HCl: λ_{max} (mμ), log ε, 327,

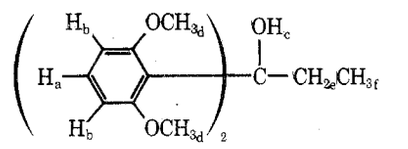
3.94; 275, 3.79; 22.6, 3.83. Uv spectrum (380 mg/l.) in 95% ethanol: λ_{max} (mμ), log ε, 293, 4.02; 260, 4.05.

Reaction of 2,6-DMPL with Methyl Isonicotinate. 2,6-DMPL [0.07 mol made from 0.1 mol of *n*-butyllithium (62.5 ml) and RDME (0.1 mol, 13.8 g)] and methyl isonicotinate (0.1 mol, 13.7 g in an equal volume of ether) were refluxed for 5 hr and processed to give RDME (2.3 g, 16.8%, bp 46–50° (0.6 mm)) and 2,6,2′,6′-tetramethoxydiphenyl-4-pyridylcarbinol, C (mp 184.0–185.4° dec from an ethanol–ethyl acetate mixture); picrate, mp 158.0–159.2° dec from ethanol. *Anal.* of C. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08. Found: C, 69.48; H, 6.07. *Anal.* of picrate of C. Calcd $C_{28}H_{26}N_4O_{12}$: C, 55.08; H, 4.29. Found: C, 55.20; H, 4.47. Ir spectrum of C in chloroform: medium O—H stretch (3396 cm^{-1}), medium C—H stretch (2961 cm^{-1}), strong aromatic and heterocyclic C=C vibrations (1579 and 1461 cm^{-1}), very strong aryl ether (1241 cm^{-1}), and very strong O—H deformation of a tertiaryalcohol (1104 cm^{-1}). Nmr spectrum of C in acetic acid.



Group	τ (ppm)	Rel intensity
a	1.73	2.1
b	2.40	1.7
c	3.20	1.9
d	3.81	3.9
e	6.94	12.0

Reaction of 2,6-DMPL with Ethyl Propionate. 2,6-DMPL [0.07 mol made from 0.1 mol of *n*-butyllithium (62.5 ml) RDME (0.1 mol, 13.8 g)] and ethyl propionate (0.1 mol, 10.2 g in an equal volume of ether) were refluxed for 5 hr and processed to give ethyl α-propionylpropionate (2.6 g, 16.4%, bp 87–89° (12 mm); lit.[26] 88–90° (12 mm)), RDME (4.6 g, 33.2%, bp 217–218° (760 mm)), and 2,6,2′,6′-tetramethoxydiphenylethylcarbinol, D (7.9 g, 35.0%, bp 110–125° (0.6 mm), mp 120.0–120.8° from 60 to 70° petroleum ether). *Anal.* of D. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.73; H, 6.97. Ir spectrum of D in carbon tetrachloride: medium O—H stretch (3572 cm^{-1}), very strong C—H stretch (2942 cm^{-1}), very strong aromatic C=C vibrations (1587 and 1471 cm^{-1}), very strong aryl ether (1250 cm^{-1}), and very strong O—H deformation of a tertiaryalcohol (1128 cm^{-1}). Nmr spectrum of D in carbon tetrachloride.



Group	τ (ppm)	Rel intensity
a	3.06	2.0
b	3.57	4.0
c	4.23	1.0
d	6.40	12.0
e	7.52	2.0
f	9.28	3.3

Reaction of 2,6-DMPL with 4-Picoline. 2,6-DMPL [0.07 mol made from 0.1 mol of *n*-butyllithium, RDME (0.1 mol, 13.8 g)], 4-picoline (0.1 mol, 9.3 g in an equal volume of ether), and methyl benzoate (0.05 mol, 6.8 g in an equal volume of ether) were allowed to react in 100 ml of refluxing ether for 5 hr and processed in the customary manner to give RDME (9.8 g, 71.0%, bp 126–129° (60.0 mm)), 4-picoline (2.1 g, 22.6%, bp 139–141° at atmospheric pressure), 4-phenacylpyridine (3.3 g, 41.8%, bp 128–133° (1.5 mm); mp 111.0–112.3°; lit.[26] 112.0–113.4°), and 7.2 g of intractable tar. The product gave a picrate, mp 165.6–167.0° (lit.[26] 167.5–168.1°).

Reaction of 2,6-DMPL with 2-Picoline, 3-Picoline, and Methylpyrazine. To a solution of 2,6-DMPL (0.07 mol) and 2-picoline (0.1 mol, 9.3 g in an equal volume of ether) which had been refluxed for 1 hr, methyl benzoate (0.1 mol, 13.6 g in an equal volume of ether) was added and the reaction mixture was refluxed for 5 hr. Processing the reaction in the regular manner gave 2.1 g (43.7%) of 2-phenacylpyridine, mp 52.6–53.4°;[21] mp of the picrate, 177.4–178.4°.[21]

From the reaction of 2,6-DMPL (0.04 mol), 3-picoline (0.1 mol, 9.3 g), and methyl benzoate (0.05 mol, 6.8 g) there was obtained 5.9 g (63.5%) of 3-picoline (bp 54° (33.0 mm)) and 2,6-dimethoxybenzophenone (7.2 g, 40.3%, mp 98.0–99.0°).[7]

From the reaction of 2,6-DMPL (0.07 mol), methylpyrazine (0.1 mol, 9.4 g), and methyl benzoate (0.1 mol, 13.6 g) there was obtained 6.5 g (47.0%) of phenacylpyrazine, mp 82.2–84.0°.[23]

Registry No.—4-Phenacylpyridine, 1620-55-9; 2-picoline, 109-06-8; 3-picoline, 108-99-6; methylpyrazine, 109-08-0; 2-phenacylpyridine, 1620-53-7; 2-phenacylpyridine picrate, 52856-27-6; phenacylpyrazine, 40061-45-8; ethyl acetate, 141-78-6; ethyl phenylacetate, 101-97-3; ethyl butyrate, 105-54-4; ethyl isobutyrate, 97-62-1; ethyl isovalerate, 108-64-5; 2,6-dimethoxyphenyl 2-pyridyl ketone picrate, 52856-28-7; 2,6-dimethoxyphenyl-3-pyridyl ketone picrate, 52856-29-8; 2′,6′-dimethoxyisobutyrophenone 2,4-DNPH, 52856-30-1; 2′,6′-dimethoxyisovalerophenone 2,4-DNPH, 52856-31-2; 2,6-DMPL, 2785-97-9; RDME, 151-10-0; B, 52856-25-4; C picrate, 52856-26-5; methyl anisate, 121-98-2; methyl isonicotinate, 2459-09-8; ethyl propionate, 105-37-3; ethyl α-propionylpropionate, 607-97-6; 4-picoline, 108-89-4.

References and Notes

(1) G. Wittig and U. Pockels, *Ber. B.*, **72**, 89 (1939).
(2) G. Wittig, "Newer Methods of Preparative Organic Chemistry," Interscience, New York, N.Y., p 579.
(3) Reference 2, p 583.
(4) H. Lettré and A. Jahn, *Ber.*, **85**, 346 (1952).
(5) A. K. Hoffmann, A. M. Feldman, and E. Gelbaum, *J. Amer. Chem. Soc.*, **86**, 646 (1964).
(6) J. C. Martin and R. G. Smith, *J. Amer. Chem. Soc.*, **86**, 2252 (1964).
(7) D. B. Limaye, *Ber. B.*, **67**, 12 (1934).
(8) D. B. Limaye and D. D. Gangal, *Rasayanam*, **1**, 64 (1936); *Chem. Abstr.*, **31**, 2182 (1937).
(9) D. B. Limaye and S. S. Shenolikar, *Rasayanam*, **1**, 93 (1937); *Chem. Abstr.*, **32**, 2096 (1938).
(10) D. B. Limaye and S. S. Talwalkar, *Rasayanam*, **1**, 141 (1939); *Chem. Abstr.*, **33**, 1968 (1939).
(11) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, 9 (1960).
(12) A. Bistrzycki and C. Herbst, *Ber.*, **36**, 2333 (1903).
(13) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1435 (1957).
(14) J. B. Strothers, *Tech. Org. Chem.*, **11**, 228 (1963).
(15) J. C. Martin and R. G. Smith, *J. Amer. Chem. Soc.*, **86**, 2255 (1964).
(16) M. J. Kamlet, Ed., "Organic Electronic Spectral Data," Vol. 1, Interscience, New York, N.Y., 1964, p 109.
(17) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N.Y., 1964, p 109.
(18) N. C. Deno, P. T. Graves, and G. Saines, *J. Amer. Chem. Soc.*, **81**, 5790 (1959).
(19) G. W. Gray, Ed., "Steric Effects in Conjugated Systems," Butterworths, London, 1958, pp 34, 46, 52, 59.
(20) M. Hammell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950).
(21) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Amer. Chem. Soc.*, **73**, 4301 (1951).
(22) C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 940 (1957).
(23) J. D. Behun and R. Levine, *J. Amer. Chem. Soc.*, **81**, 5157 (1959).
(24) D. B. Limaye and I. Ghate, *Rasayanam*, **1**, 39 (1936); *Chem. Abstr.*, **31**, 2182 (1937).
(25) H. Gilman, H. B. Willis, T. H. Cook, F. J. Webb, and R. N. Cook, *J. Amer Chem. Soc.*, **62**, 667 (1940).
(26) S. M. McElvain, *J. Amer. Chem. Soc.*, **51**, 3124 (1929).
(27) C. D. Hurd and C. L. Thomas, *J. Amer. Chem. Soc.*, **58**, 1240 (1936).