Experimental Section

1-Methyl-4-piperidone (III).—Methyldi(β-carbethoxyethyl)-amine was prepared by the Michael addition of methylamine to ethyl acrylate, 78% yield, bp 117–119° (0.5 mm) [lit.[25] reports bp 118–119° (0.5 mm)]. The latter underwent a Dieckmann condensation with potassium *tert*-butoxide to give the cyclic β-keto ester, which upon hydrolysis and decarboxylation yielded 1-methyl-4-piperidone, bp 67–79° (19 mm), n^{24}D 1.4580 [lit.[26] reports mp 56–58° (11 mm), n^{25}D 1.4580, yield 58%].

1-Acetyl-4-piperidone.—A Michael addition of ammonia to ethyl acrylate gave di(β-carbethoxyethyl)amine, bp 154–164° (1.5 mm) [lit.[27] bp 150–164° (1–2 mm)]. The *N*-benzoyl derivative was prepared and had bp 192–197° (0.4 mm), n^{24}D 1.5020 [lit.[27] bp 192–194° (0.4 mm), n^{25}D 1.5040]. The Dieckmann reaction was then carried out with the aid of sodium and furnished 1-benzoyl-3-carbethoxy-4-piperidone, mp 59–60° (lit.[27] mp 54–56°).

4-Piperidone hydrochloride was prepared by hydrolysis of the previous compound by refluxing with 6 *N* hydrochloric acid until carbon dioxide evolution ceased. The solution was filtered to remove the benzoic acid, and the product was taken up in ether. The ether solution was evaporated to dryness and the product was decolorized with charcoal and crystallized from ethanol–ether. It was then taken up in acetic acid–sodium acetate and acetylated with acetic anhydride, bp 135–136° (0.3 mm), n^{25}D 1.5016 [lit.[28] reports bp 124–128° (0.2 mm), n^{25}D 1.5023].

Dipole Moments.—The apparatus and method[29] and the details of the computations[30] have all been described previously, no allowance for atomic polarization being made in line with earlier conclusions.[31]

Registry No.—III, 1445-73-4; IV, 32161-06-1; *N*-methylpiperidine, 626-67-5; *N*-acetylpiperidine, 618-42-8.

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Notes

Friedel–Crafts Acylation of 10-Methylphenothiazine

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As part of the preparation of a compound containing the 3-(10-methylphenothiazinyl) group, it was necessary to use a Friedel–Crafts acylation in one of the synthetic steps. Although hundreds of phenothiazine compounds have been reported we were unable to find a high-yield procedure for the Friedel–Crafts acylation of 10-methylphenothiazine.

The literature reports that *N*-alkylphenothiazine is 3,7 directing and *N*-acylphenothiazine is 2,8 directing in Friedel–Crafts acylation.[1–6] Both mono- and disubstituted products are formed but were not separated in the reported crude yields. Acylation takes place with higher yields with *N*-acylphenothiazine than with *N*-alkylphenothiazine.

For example, when 1 mol of 10-methylphenothiazine was acylated with 1 mol of acetyl chloride in carbon disulfide with aluminum chloride, the crude yield of 3-acetyl product was 25% (reported as the hydrate) with 42.5% utilization of 10-methylphenothiazine.[1] In a recent attempt to duplicate the reaction, the major product found was the 3,7-diacetyl derivative.[2] With 2.5 mol of acetic anhydride, the yield of 3,7-diacetyl product was 39%.[3]

Acylation of 10-acetylphenothiazine with 1 mol of β-carbomethoxypropionyl chloride in carbon disulfide with aluminum chloride gave 58% of crude 2-acylated product.[5] A 94% yield of the 2-acetyl product was obtained using 1 mol of acetic anhydride,[6] while the 2,8-diacetyl derivative was obtained in 52% yield using 4 mol of acetyl chloride.[3]

Results and Discussion

In this laboratory, it was found that the aluminum chloride–carbon disulfide system gave rather poor yields of monosubstituted product in the acylation of 10-methylphenothiazine with β-carbomethoxypropionyl chloride. The effect of solvent and catalyst on the reaction was therefore investigated; the results are summarized in Tables I and II and Chart I.

The 3 position of the substituent is assigned by analogy to related cases[1,3,7] and the nmr spectra. The chemical shift of the aromatic protons in **4** (τ 2.18, 2.27, 3.14 for a_1, a_2, and b) agree well with those calculated for a 3-acyl-, 5-alkylthio-, 6 dialkylamino-substituted benzene (τ 2.19, 2.22, 3.34), using a recent table of aromatic chemical shifts,[8] but not for the corresponding 2-acyl derivative (τ 2.70, 2.72, 2.77).

Product **5** presumably arises by acylation of a second mole of phenothiazine by the monosubstituted product, leading to the tertiary alcohol which dehydrates to **5**. Compound **5** gave a single peak in thin

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TABLE I

FRIEDEL–CRAFTS REACTIONS. YIELDS OF PRODUCTS AS A FUNCTION OF CATALYST, SOLVENT, AND REACTION CONDITIONS

Mol of catalyst[a]	Solvent	Time, hr	Temp, °C	Recovered mol of 1	3	4	5	Yield of 3,[f] %
0.1 H_2SO_4	*c*	3.5	70		0.00			
0.1 H_2SO_4	CS_2	3.5	40		0.00			
2 $AlCl_3$	*c*	3.5	70		<0.05[b]	>0.10[b]	>0.10[b]	
2 $AlCl_3$	CS_2	3.5	40		<0.05[b]	>0.10[b]	>0.10[b]	
0.7 $AlCl_3$	$CHCl_3$	0.6	64	0.41	0.06	0.21	0.14	10
0.3 $AlCl_3$	$CHCl_3$	1.4	45	0.60	0.08	0.15	0.03	20
0.5 $ZnCl_2$	*c*	1.5	75	0.00	0.16			16
0.5 $ZnCl_2$	CS_2	4.0	46	0.82	0.07	0.02	0.02	39
2 $ZnCl_2$	CS_2	4.0	48	0.71	0.14	0.03	0.02	49
0.4 $ZnCl_2$	*d*	1.0	95		Tars			0
0.4 $ZnCl_2$	*e*	0.5	82	0.44	0.37	0.10	0.03	66
0.4 $ZnCl_2$	$CHCl_3$	4.5	63	0.55	0.36	0.02	0.01	80

[a] Based on 1 mol of **1** plus 1 mol of **2**. [b] Estimated from thin layer chromatography. [c] Nitrobenzene. [d] *sym*-Tetrachloroethane. [e] *sym*-Dichloroethane. [f] Yield of **3** based on 10-methylphenothiazine reacted.

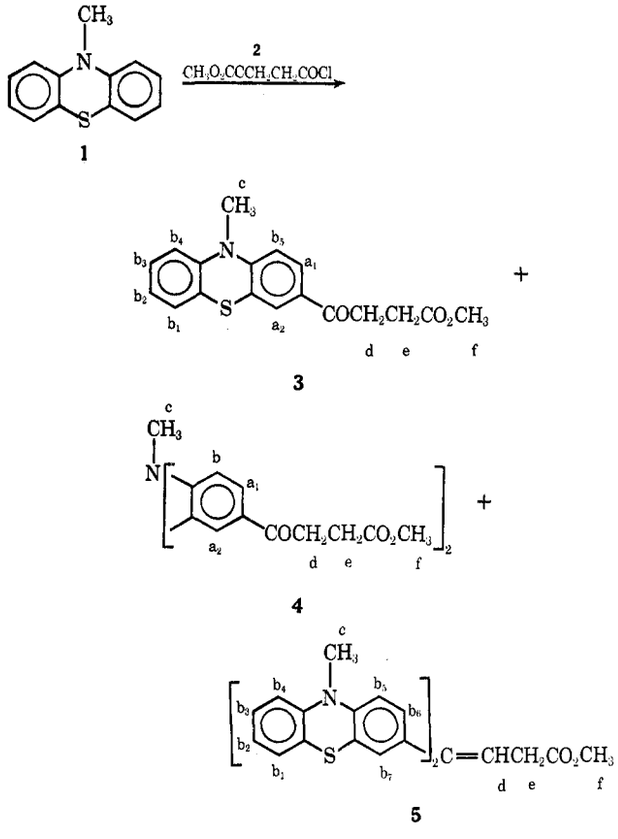
TABLE II

NMR SPECTRA OF COMPOUNDS

Compd	H	Area	τ, ppm	*J*, cps
3	a_1, a_2	2	2.19 (d)[a], 2.28 (s)[b]	8.5, 2.0
	b_{1-5}	5	2.60–3.30 (m)	
	c	3	6.60 (s)	
	d	2	6.78 (t)	6.0
	e	2	7.25 (t)	6.0
	f	3	6.29 (s)	
4	a_1, a_2	4	2.18 (d)[a], 2.27 (s)[b]	9.0, 2.0
	b	2	3.14 (d)	8.5
	c	3	6.56 (s)	
	d	4	6.76 (t)	6.0
	e	4	7.25 (t)	6.0
	f	6	6.28 (s)	
5	b_{1-7}	14	2.66–3.42 (m)	
	c	2	6.71 (s)	
		4	6.67 (s)	
	d	1	3.90 (t)	7.5
	e	2	6.88 (d)	7.5
	f	3	6.30 (s)	

[a] Ortho and meta splitting. [b] Meta splitting not visible because of overlap.

CHART I



layer chromatography; analysis and nmr confirmed the gross structure assignment and mechanism of formation. However, the glassy nature of **5** and the presence of two NCH_3 peaks in the nmr spectrum which did not coalesce or move together up to 90° indicate that this product is not a single compound. The nmr data suggest the possibility of conformational isomers with a high energy barrier to rotation, but this is not proven.

Catalysts and Solvents.—Sulfuric acid does not act as a catalyst for the acylation. With aluminum chloride the solution became red immediately; this is probably a reaction of the catalyst with the electron donor, 10-methylphenothiazine, to form an oxidized complex.[9] Also, there was much black tar, indicating further side reactions on the monoacylated and vinyl products. Yields improved with lower aluminum chloride levels, and by use of chloroform instead of carbon disulfide or nitrobenzene. With $AlCl_3$, **4** is produced in better yield than **3**, and in many cases **5** is also present in higher yield than **3**.

Zinc chloride is insoluble in all the solvents used. In nitrobenzene or carbon disulfide, black tars formed on the surface of the catalyst, and the reaction rate is therefore reduced considerably by blockage of the surface. The initial product, **3**, insoluble in these solvents, remained on the surface of the zinc chloride and thus was available for further reactions which eventually produced tars. In chlorinated solvents, however, the reaction product, **3**, was dissolved from the zinc chloride surface, and the zinc chloride stayed clean and active. This also led to a better yield, since the amount of side reaction was reduced. At 95° (run 10) only tars were obtained; the reaction proceeded too far. With $ZnCl_2$ catalyst, the relative amounts of products formed were vastly different from reactions in which $AlCl_3$ was

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used. The monoacylated product, **3**, predominated. This indicates that $ZnCl_2$ is operating by a somewhat different mechanism than $AlCl_3$.

In general it seems that aluminum chloride is too active a complexing agent with 10-methylphenothiazine. While complexed with 10-methylphenothiazine, aluminum chloride probably prevents acylation; therefore acylation tends to take place on uncomplexed material. As the monoacylated product is less basic than 10-methylphenothiazine, it tends to be uncomplexed and is therefore preferentially acylated. This leads to multiple acylations and correspondingly poor yields of monoacylated product. Also, complexed **3** can acylate starting material to produce **5** and is removed by that path as well. In the case of 10-acylphenothiazine, the acyl group reduced the electron-donating properties of the phenothiazine and therefore reduces the strength of the complex with aluminum chloride. This can account for the better acylation yields for this compound reported in the literature.

Acylation apparently takes place on the surface of the insoluble zinc chloride. However, solvents such as chloroform can remove the acylated product and reduce secondary reactions. Another factor in favor of zinc chloride is that it is too weak a Lewis acid to complex irreversibly with the products. While this lowers reaction rates, they now tend to be related to the reactivity of the starting materials. Since the acid chloride and 10-methylphenothiazine are the most reactive materials present, formation of **3** is favored.

Experimental Section

10-Methylphenothiazine.—A method was used which is more convenient but similar in principle to those methods in the literature.[1,10] In this case, the strong base for removing the N proton from phenothiazine was made and used immediately in the same reaction vessel. Sodium (23 g, 1 g-atom) was added slowly in small pieces to 500 ml of dimethyl sulfoxide[11,12] under nitrogen with cooling to below 40° and stirring. After all of the metal had reacted, 100 g (0.5 mol) of phenothiazine was added slowly to maintain a temperature of 40°. Methyl iodide (142 g, 1 mol) was then added dropwise at 40°. The product was precipitated in water, filtered, and dried. The crude material, 107 g, was then chromatographed on a 1 × 30 in. silica gel column. The material eluted with benzene was recrystallized twice from ethanol–acetone (4:1), yield 91 g (86%), mp 97–100° (lit.[13] mp 99.5°).

Typical Procedure for Friedel–Crafts Reaction.—Chloroform was washed with water, and then dried over anhydrous calcium sulfate. Dry chloroform (700 ml), 85 g (0.4 mol) of 10-methylphenothiazine, and 60 g (0.4 mol) of β-carbomethoxypropionyl chloride[14] were mixed. Anhydrous zinc chloride (22 g, 0.16 mol) was added and the flask was heated to reflux at 63° with stirring for 4.5 hr. Formation of products was followed by thin layer chromatography in order to optimize the amount of monoacylated product. The reaction was quenched by cooling and addition of ice. After washing with water, the chloroform solution was evaporated. The products were dissolved in a minimum amount of benzene and chromatographed on a 1 × 28 in. silica gel column. Elution solvents were first benzene, then chloroform, then ethyl acetate. The eluted solvent was divided into 100-ml portions, which were evaporated separately. Separation of compounds was checked by tlc, and fractions containing two components were rechromatographed.

Unreacted 10-methylphenothiazine was eluted in the first 300 ml of benzene. There was a slight overlap with compound **5**. After rechromatographing, recovered 1 weighed 47 g (0.218 mol).

Methyl 4,4-Bis(10-methyl-3-phenothiazinyl)butene-3-oate (5) (Probable Assignment).—Compound **5** was eluted with benzene in the 300–1000-ml fractions. The fractions which overlapped with **1** were rechromatographed on silica gel with benzene. In drying, an amorphous, glassy solid, **5**, was obtained which had a single peak in tlc, weight 2.18 g (0.0042 mol).

Anal. Calcd for $C_{31}H_{26}N_2S_2O_2$: C, 71.4; H, 4.97; N, 5.36. Found: C, 71.36; H, 5.00; N, 5.56.

Methyl 4-(10-Methyl-3-phenothiazinyl)-4-oxobutanoate (3).—Elution of the column with 800 ml of 50:50 chloroform–benzene and 500 ml of $CHCl_3$ and solvent evaporation then produced **3**, crude yield 47 g (0.145 mol). **3** was first recrystalllzed from cyclohexane–benzene (2:1) and then from methanol–acetone (2:1), mp 113–116° (half width on a Du Pont 900 DTA at 20°/min).

Anal. Calcd for $C_{18}H_{17}SNO_3$: C, 66.1; H, 5.20; N, 4.28. Found: C, 66.07; H, 5.21; N, 4.41.

Dimethyl 4,4′-(10-Methyl-3,7-phenothiazinylene)di(4-oxobutanoate) (4).—Further elution of the column with 800 ml of chloroform eluted a yellow band of **4** in substantially pure form. It was recrystallized from 50:50 methanol–acetone, weight 2.36 g (0.0054 mol), mp 142–145°.

Anal. Calcd for $C_{23}H_{23}NO_6S$: C, 62.6; H, 5.21; N, 3.17. Found: C, 62.46; H, 5.22; N, 3.24.

Registry No.—**1**, 1207-72-3; **3**, 33214-29-8; **4**, 33214-30-1; **5**, 33214-31-2; $AlCl_3$, 7446-70-0; $ZnCl_2$, 7646-85-7.

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The Reaction of 4- and 5-Acetyloxazoles with Malononitrile

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Ring opening of oxazoles with nucleophilic reagents such as ammonia,[1-4] hydroxide,[5] and 2,4-dinitrophenylhydrazine[6] has been reported. We now wish to report the facile ring opening and subsequent recyclization of 4- and 5-acetyloxazoles with the nucleophile, malononitrile, in the presence of a base.

When 4-acetyl-2,5-dimethyloxazole[7] (**1**, R = CH_3) is allowed to react with 1 mol of malononitrile in the presence of potassium acetate, a small yield of the expected dicyanovinyl condensation product (**2**, R = CH_3) can be isolated. However, when 1 or 2 mol of malononitrile reacts with the acetyloxazole in the presence of sodium hydroxide, **2** is not obtained, but a different,

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