Heterocycles from Substituted Amides. VI (1,2). A New Carbostyril Synthesis from *alpha*-Substituted Acetamides and the Vilsmeier Reagent

John P. Chupp and Suzanne Metz*

Monsanto Agricultural Products Company, Research Department,
800 N. Lindbergh Blvd., St. Louis, Missouri 63166

Received May 1, 1978

Reaction of tertiary α-substituted acetanilides with Vilsmeier reagent has been found to give 1,3-disubstituted-carbostyrils, **1**. α-Chloro-*N*-(1-cyclohexen-1-yl)acetamides are similarly converted to tetrahydro carbostyrils **2** and **3**. The method appears useful for the preparation of a variety of 1,3-substituted 2(1*H*)quinolinones. The scope and mechanism of the reaction has been investigated, with evidence presented to indicate the ring-closure proceeds *via* electrophilic attack of Vilsmeier reagent on intermediate chlorenamine.

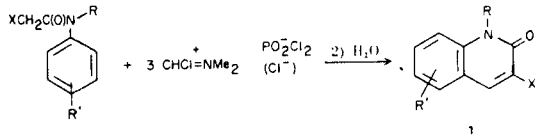
J. Heterocyclic Chem., 16, 65 (1979).

Reviews of the literature (3-5) as well as individual papers (6-9) readily reveal that Vilsmeier reagents as well as the dichloro derivatives (phosgene immonium salts) can be utilized in various heterocyclic syntheses. When carbamoylmethyl groups are treated, a chlorenamine derivative is generally postulated as forming (3,9,10). If there is no adjacent nucleophilic center, hydrolysis can give the commonly derived formyl moiety (enol or keto form), or sometimes the dimethylamine derivative of the

enol. However, ring-closures can occur when the generated electrophilic center condenses intramolecularly at a suitably adjacent nucleophilic site (3).

alpha-Substituted acetanilides are readily available materials that would appear to satisfy the above requirements for heterocyclic synthesis. Indeed contacting suitable α-substituted acetanilides with excess Vilsmeier or Arnold reagent (11) give rise to carbostyrils as shown in Scheme 1 and Table I.

Scheme 1 (a)

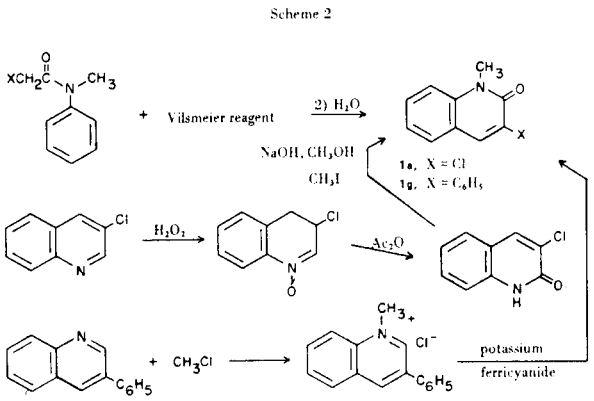


(a) See Table I for structure definition.

Structural confirmation is afforded by the facile preparation of **1a** and **1g** in one step from the appropriately substituted acetanilide. Although low yields can be encountered, fair amounts of carbostyrils are generally obtained in an essentially one step procedure. Compounds **1a** (12) and **1g** (13) were previously available only by a multistep route from the appropriate quinolines as shown in Scheme 2.

With the exception of secondary (N-H) anilides (where tars are largely obtained), carbostyril formation readily occurs with higher *N-primary*-alkyl substitution. Treatment of α-chloro-*N-isopropyl*-acetanilide with Vilsmeier

Scheme 2



reagent however, leads to a number of chlorinated anilides and enamines; the major components being the α,α,α-trichloro-*N*-isopropylacetanilides, their respective phenyl ring-chlorinated counterparts, and *N*-isopropyl-*N*-(trichlorovinyl)chloroaniline. Structures for these products are based upon ms examination of a distilled sample subjected to glc separation. The chlorinated anilides are unequivocal. When it occurred, ring chlorination was determined by ready appearance of the $Cl\text{-}C_6H_4NHCO^+$ ion at 154 as well as the chlorophenyl ion. The number of chlorine atoms in each molecular ion is unambiguous due to the characteristic chlorine isotope ratios. In addition, authentic α,α-di- and α,α,α-trichloroacetanilides were determined to have the same glc retention times and mass spectra as those identified in the mixture.

Chloroenamine formation is entirely reasonable, considering the chlorination products that arise from action of phosphorus chlorides on chloracetamides (14), or alternatively, the known deoxygenating ability of Vilsmeier reagent on certain previously studied amides (3), discussed earlier.

The most significant finding in attempting to prepare 1-isopropyl-3-chlorocarbostyril from 2-chloro-*N*-isopropylacetanilide is that none of this product is seen at all; rather chlorination takes place either directly or through enamine intermediates, without ring closure. Thus, the isopropyl group exerts considerable steric inhibition to carbon-carbon bond making. If chlorination is accom-

0022-152X/79/010065-07$02.25

Table I

Carbostyrils (1) and Tetrahydrocarbostyrils (2,3)

Material	R	X	R′	Yield (%)	M.p. (b.p.) (°C)	Pertinent Spectral Data: Nmr (a), δ Hetero-Olefin Proton	Nmr (a), δ N-CH_3 (angular CH_3)	Nmr (a), δ Other	Uv (EtOH) λ (max)	Uv (EtOH) ε max
1a	CH_3	Cl		46	145-146	7.84	3.78		334	(7,500)
b	C_2H_5	Cl		55	118-119	7.72			334	(8,600)
c	C_2H_5	Cl	6-Cl	67	195	8.01 (b)				
d	CH_3	Cl	7-CH_3	43	224-227	8.10 (c)	3.90	2.50 (ArCH_3)	335	(10,700)
e	CH_3	Cl	6-CH_3	28	160-162	7.88	3.80	2.43 (ArCH_3)		
f	CH_3	Cl	6-CH_3O	22	133-135	7.90	3.80 or 3.95	3.95 or 3.80 (CH_3O)		
g	CH_3	C_6H_5		40	137-138	7.70	3.7		340	(11,300)
h	CH_3	CH_3O		6	140.5-143	7.00	4.2 or 3.8	3.8 or 4.2 (CH_3O)	318	(13,500)
i	CH_3	CH_3S		23	104-106	7.25	3.70	2.4 (CH_3S)	336	(7,700)
j	CH_3	$C_6H_5N(CH_3)SO_2$-		2	173-176	8.44	3.7 or 3.8	3.8 or 3.7 $\left(\begin{matrix}CH_3N\\ \\ C_6H_5\end{matrix}\right)$	352	(6,300)
2a	CH_3		H	12	110-112	7.35	3.60		325	(9,900)
b	$C_2H_5OC_2H_4$		H	57	65-66	7.20				
c	C_6H_5		H	9	175-176	(d)		(d)		
d	CH_3		Cl	43	134-136	7.39	3.75	5.18 ($C\!<^{H}_{Cl}$)	326	(9,900)
3a	H			19	[122 (0.05 mm)] 55-57	6.60	3.25 (1.30)	5.26 (t, =CH)	298	(2,000)
b	CH_3			44	[125-148 (0.1 mm)]	6.45	3.20 (1.15)	1.62 (s, =CCH_3)	283	(2,900)

(a) Deuteriochloroform. (b) Deuteriochloroform-D_6MSO. (c) Nmr in D_5 pyridine. (d) See Experimental for detailed nmr.

Table I (Supplement)

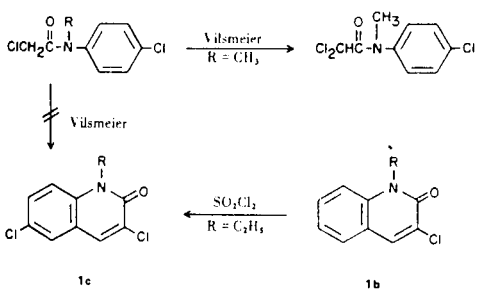
Carbostyrils (1) and Tetrahydrocarbostyrils (2,3)

Material	R	X	R′	Empirical Formula	Elemental Analyses Percentage Composition Calcd. C	Calcd. H(Cl)	Calcd. N	Found C	Found H(Cl)	Found N
1a	CH_3	Cl		$C_{10}H_8ClNO$	62.03	4.16	7.23	62.00	4.22	7.24
b	C_2H_5	Cl		$C_{11}H_{10}ClNO$	63.62	(17.07)	6.75	63.59	(17.13)	6.77
c	C_2H_5	Cl	6-Cl	$C_{11}H_9Cl_2NO$	54.57	(29.29)	5.79	54.49	(29.46)	5.79
d	CH_3	Cl	7-CH_3	$C_{11}H_{10}ClNO$	63.62	4.85	6.75	63.68	4.88	6.84
e	CH_3	Cl	6-CH_3	$C_{11}H_{10}ClNO$	63.62	4.85	6.75	63.65	4.86	6.77
f	CH_3	Cl	6-CH_3O	$C_{11}H_{10}ClNO_2$	59.07	4.51	6.26	58.98	4.57	6.26
g	CH_3	C_6H_5		$C_{16}H_{13}NO$	81.68	5.57	5.95	81.54	5.51	5.93
h	CH_3	CH_3O		$C_{11}H_{11}NO_2$	69.83	5.86	7.40	69.58	5.87	7.42
i	CH_3	CH_3S		$C_{11}H_{11}NOS$	64.36	5.40	6.82	64.40	5.41	6.88
j	CH_3	$C_6H_5N(CH_3)SO_2$-		$C_{17}H_{16}N_2O_3S$	62.18	4.91	8.53	61.90	4.95	8.59
2a	CH_3		H	$C_{10}H_{12}ClNO$	60.76	6.12	7.09	60.81	6.15	7.04
b	$C_2H_5OC_2H_4$		H	$C_{13}H_{18}ClNO_2$	61.05	(13.86)	5.48	61.02	(14.21)	5.41
c	C_6H_5		H	$C_{15}H_{14}ClNO$	69.36	(13.65)	5.39	69.32	(13.72)	5.42
d	CH_3		Cl	$C_{10}H_{11}Cl_2NO$	51.74	4.78	6.03	51.80	4.82	6.08
3a	H			$C_{11}H_{14}ClNO$	62.41	6.67	6.62	62.16	6.71	6.58
b	CH_3			$C_{12}H_{16}ClNO$	63.85	7.14	6.21	63.70	7.19	6.17

plished by a positive chlorinium (Cl^+) ion, some reduction of Vilsmeier reagent must take place to furnish such a chlorinating species.

Apparently, nuclear chlorine deactivates the ring sufficiently in 2,4′-dichloro-*N*-methylacetanilide to preclude cyclization, with again, only chlorination taking place as evidenced by formation of 2,2,4′-trichloro-*N*-methylacetanilide. 1-Ethyl-3,6-dichlorocarbostyril **1c**, however, can be prepared by chlorination of **1b** in sulfuryl chloride solution (Scheme 3).

Scheme 3

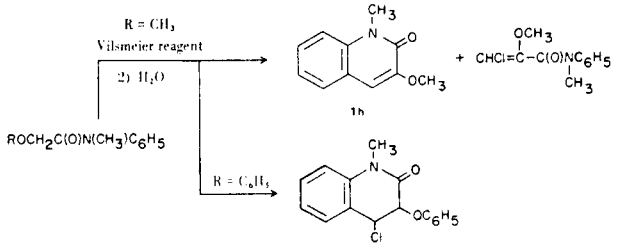


Activating groups as represented by *meta* and *para*-methyl and methoxy groups allow cyclization to carbostyrils, although these same groups in the *ortho* position hinder such formation. 2-Chloro-*N*-methyl-acet-*o*-toluidide upon reaction with Vilsmeier reagent gave 2,2-dichloro-*N*-methylacet-*o*-toluidide, but no carbostyril.

Some activation of the *alpha*-methylene by a suitable *alpha*-substituent appears necessary. *N*-Methylacetanilide fails to give product. On the other hand, having an activating group in such a position does not guarantee isolation of carbostyril product. Further, 2-bromo-*N*-methylacetanilide was converted to **1a** with Vilsmeier reagent, demonstrating smooth halogen interchange.

Although the carbostyril **1h** was isolated from the action of Vilsmeier reagent on *N*-methyl-2-methoxyacetanilide, another neutral material identified by ir, nmr, ms, and analysis proved to be 3-chloro-*N*-methyl-2-methoxyacrylanilide. *N*-methyl-2-phenoxyacetanilide upon reaction with Vilsmeier reagent gave the cyclic product, 4-chloro-1-methyl-3-phenoxy-3,4-dihydrocarbostyril (Scheme 4).

Scheme 4



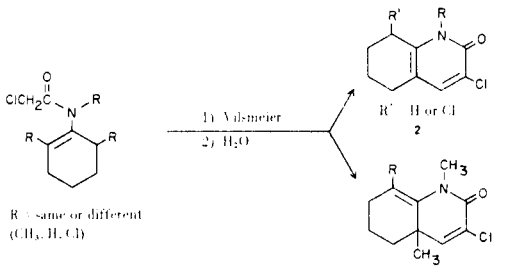
In addition to the aromatic absorptions, the 3 and 4-protons in the phenoxyl compound were found at δ 6.4 and 6.66 as two separated absorptions, each possessing fine ($J < 0.5$ Hz) splitting. The products arising from the two ether amides here could have similar precursors (see discussion of Scheme 6 below).

In addition to anilides serving as substrates it became of interest to investigate certain *N*-(1-cyclohexen-1-yl)-acetamides. These materials are structurally related to the anilides, in that an available 2-position is susceptible to electrophilic substitution. Such electrophilic ring-closures have been heretofore demonstrated by formation

of tetrahydrothioquinazolinediones and -indazolinones from *N*-(1-cyclohexen-1-yl)carbamoyl chlorides *via* carbamoyl isothiocyanate and azide intermediates (15,16).

Contacting various tertiary α-chloro-*N*-(1-cyclohexen-1-yl)acetamides with excess Vilsmeier reagent can give rise to either 5,6,7,8-tetrahydro carbostyrils **2**, or 4a,5,6,7-tetrahydro carbostyrils **3**. This alternative product formation is wholly dependent on the amount and kind of ring substitution found in the parent cyclohexenyl amide (Scheme 5).

Scheme 5 (a)



R = same or different (CH3, H, Cl)

(a) See Table I for structure definition.

Structure of **2** and **3** are verified by the method of synthesis, ir. analysis, and particularly, to differentiate between **2** and **3**, uv and pmr. Only the conjugated carbostyrils **1** and **2** have a characteristic uv absorption maximum between 318-340 mμ. In **3**, nmr spectra display the upfield angular methyl group and either an olefinic-proton or -methyl group. In materials **1** and **2** the methylamino group is found downfield at *ca.* δ 3.7-3.9, while in the unconjugated compounds **3**, this moiety is found upfield at δ 3.1-3.25. Pertinent uv and nmr data are given in Table I.

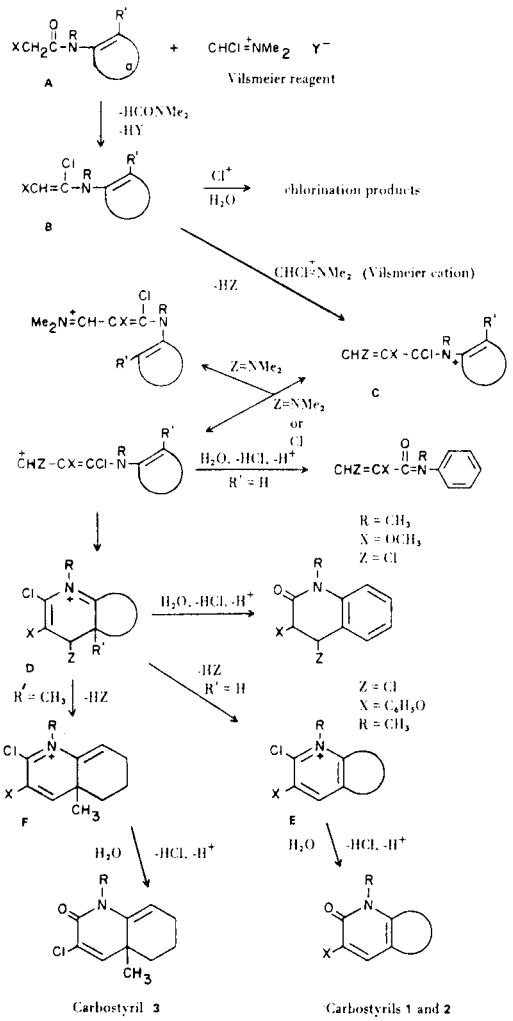
The ring-closure onto the "*ortho*" position in α-chloro-*N*-(6-chloro-1-cyclohexen-1-yl)-*N*-methylacetamide (Scheme 5, Table I) would not seem unusual in view of the steric inhibition to cyclization in the aromatic series. More surprising was the preferential ring-closure on the methyl-substituted *beta*-carbon in reaction of Vilsmeier reagent with either 2-chloro-*N*-methyl-*N*-(2-methyl-1-cyclohexen-1-yl)acetamide or 2-chloro-*N*-methyl-*N*-(6-methyl-1-cyclohexen-1-yl)acetamide, to give the angularly-substituted tetrahydrocarbostyril **3a**. Indeed, a higher yield of **3b** was found, obtained from the seemingly more hindered 2-chloro-*N*-(2,6-dimethyl-1-cyclohexen-1-yl)-*N*-methylacetamide. The favored formation of 4a,5,6,7-tetrahydrocarbostyrils, **3**, with angular substituents apparently overcomes steric inhibitions found important in the anilide series.

Finally, in a competitive system represented by 2-chloro-*N*-(1-cyclohexen-1-yl)acetanilide, the *beta*-carbon in a 1-cyclohexene system is more receptive to electrophilic attack than the *ortho*-position of the aniline ring, with formation of **2c**, 3-chloro-1-phenyl-5,6,7,8-tetrahydrocarbostyril. A similar preference was previously observed in the synthesis of 1-phenyltetrahydroindazolin-3-one from pyrolysis of *N*-(1-cyclohexen-1-yl)carbaniloyl azides (15).

Scheme 6 outlines the reaction of α-substituted amides, **A**, with Vilsmeier reagent, to give the various products encountered in the present study. The mechanism envisages reaction of Vilsmeier reagent at the carbonyl oxygen in **A**, converting the material to a chlorenamine **B**, consistent with certain references (3,8) and results discussed above; the need for *alpha*-proton activation by group X is seemingly necessary to induce enolization prior to formation of **B**.

The latter is a dienamine with two activated *beta*-carbons. Although either electron rich center could presumably react with the Vilsmeier electrophile, Scheme 6 shows only reaction at the exo-cyclic position to give resonance stabilized iminium ion **C**. The isolation of 3-chloro-*N*-methyl-2-methoxyacrylanilide could follow

Scheme 6 (a,b,c)



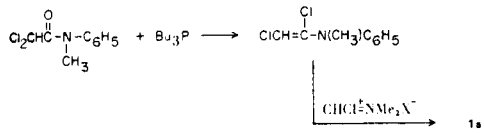
(a) a = Residual portion of phenyl or cyclohexene ring. (b) Z = Cl^- or NMe_2^-. (c) Y = Cl^- or $PO_2Cl_2^-$.

directly from hydrolysis of **C**.

Cyclization of **C** gives **D**, the latter serving as the immediate precursor of 4-chloro-1-methyl-3-phenoxy-3,4-dihydrocarbostyril. Loss of HZ [HCl or $NH(CH_3)_2$] from **D** gives resonance stabilized quinolinium salts **E** and **F**. Hydrolysis of these materials would readily give **1**, **2** and **3**, respectively.

If Scheme 6 is a close approximation of the actual mechanism, than a known enamine such as *N*-(1,2-dichlorovinyl)-*N*-methylaniline (14) (material **B**, R = CH_3, X = Cl) should react with Vilsmeier reagent to produce carbostyril after hydrolysis. In fact nearly comparable yields of **1a** was obtained using only two rather than the optimum three moles of Vilsmeier reagent with this enamine (Scheme 7).

Scheme 7



Since the distilled chlorenamine is known to be highly unstable and may have contained starting 2,2-dichloro-*N*-methylacetanilide (a material which was shown to remain unchanged when subjected to the Vilsmeier reagent), this conversion is accepted as supporting evidence for the proposed mechanism.

EXPERIMENTAL

The spectra obtained were recorded from a Perkin-Elmer Infracord (ir), Varian T-60 NMR spectrometer, Beckman DK-2A (uv) and CH-7A mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and Atlantic Microlab, Inc., Atlanta, Georgia.

Procedures for the preparation of starting 2-chloro-*N*-(1-cyclohexen-1-yl)acetamides (17,18) and representative compounds **1**, **2** and **3**, contained in Table I, as well as other key materials described in the text, are given below:

2-Chloro-*N*-(1-cyclohexen-1-yl)-*N*-methylacetamide.

Chloracetyl chloride (78 g., 0.69 mole) was added cautiously to 300 ml. of a toluene solution containing 76.3 g. (0.69 mole) of *N*-cyclohexylidene-*N*-methyl amine (19). The mixture was heated at reflux in excess of three hours, then cooled, and washed with 10% sodium carbonate solution. After drying the toluene solution over magnesium sulfate, solvent was removed and the residue vacuum distilled at b.p. 100-108° (0.2 mm) to give 87.3 g. The solidified distillate was recrystallized from hexane, m.p. 45-46°; nmr (carbon tetrachloride): δ 1.6-2.6 (multiplets, 8, cyclohexyl protons), 3.15 (s, 3, N-C*H*$_3$), 4.2 (s, 2, ClC*H*$_2$CO), 5.8 (1, m =C*H*).

Anal. Calcd. for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.79; H, 7.57; N, 7.05.

2-Chloro-*N*-(6-chloro-1-cyclohexen-1-yl)-*N*-methylacetamide.

2-Chloro-*N*-(1-cyclohexen-1-yl)-*N*-methylacetamide (6.7 g., 0.0358 mole) was dissolved in 100 ml. of carbon tetrachloride and 0.037 mole of chlorine (2.6 g. contained in 70 ml. of carbon tetrachloride) added with cooling. The reaction mixture was then heated at 60° for one half hour, then vacuum treated to remove both gaseous hydrogen chloride and solvent. The residue was recrystallized from hexane to give 4.7 g., m.p. 79-80°; nmr (deuteriochloroform): δ 1.7-2.6 (m, 6, 3,4,5-cyclohexenyl protons), 3.15 (s, 3, NC*H*$_3$), 4.22 (s, 2, ClC*H*$_2$), 4.7 (m, 1, 6-cyclohexenyl proton), 6.1 (m, 1, =CH).

Anal. Calcd. for $C_9H_{13}Cl_2NO$: C, 48.67; H, 5.90; N, 6.31; Cl, 31.92. Found: C, 48.63; H, 5.94; N, 6.08; Cl, 31.45.

2-Chloro-*N*-(2-methyl-1-cyclohexen-1-yl)-*N*-methylacetamide.

This compound was prepared in refluxing toluene from equimolar amounts of *N*-cyclohexylidene-*N*-2-dimethyl amine (19) and chloracetyl chloride. The material was obtained in 71% yield, b.p. 115-130° (0.2 mm) and contained as shown by nmr, 93% of the 2-methyl and 7% of the 6-methyl compound. (see below); nmr (deuteriochloroform): δ 1.6 (s, 3, =CC*H*$_3$), 1.6-2.4 (multiplets, 8, cyclohexyl protons), 3.0 (s, 3, N-C*H*$_3$), 4.0 (s, 2, ClC*H*$_2$CO).

Anal. Calcd. for $C_{10}H_{16}ClNO$: Cl, 17.58; N, 6.94. Found: Cl, 17.31; N, 6.89.

2-Chloro-*N*-(6-methyl-1-cyclohexen-1-yl)-*N*-methylacetamide.

N-(Cyclohexylidene)-*N*,2-dimethyl amine (32 g., 0.255 mole), in 200 ml. of toluene was cooled to -50° and 30 g. (0.266 mole) of chloracetyl chloride added, followed by 26 g. (0.26 mole) of triethyl amine. With stirring, the mixture was allowed to reach room temperature, and the amine salt filtered. The filtrate was washed with water, dried over magnesium sulfate. After vacuum removal of solvent, the residual solid was recrystallized from cold pentane to give crystals, m.p. 36.5-38°; nmr (deuteriochloroform): δ 1.02 (d, 3, J = 7 Hz, C*H*$_3$), 1.56-2.6 (m's, 7, cyclohexyl protons), 3.1 (s, 3, NC*H*$_3$), 4.2 (s, 2, ClC*H*$_2$CO), 5.8 (m, 1, =C*H*).

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.55; H, 8.00; N, 6.94; Cl, 17.58. Found: C, 59.50; H, 7.89; N, 7.06; Cl, 17.84.

2-Chloro-*N*-(2,6-dimethyl-1-cyclohexen-1-yl)-*N*-methylacetamide.

N,2,6-trimethyl-*N*-(cyclohexylidene) amine (19) (0.115 mole) was placed in 200 ml. of chlorobenzene with 13 g. of chloracetyl chloride. After three hours at reflux the material was vacuum treated to remove chlorobenzene, and the residue taken up in ether, washed twice with water and the resulting organic layer dried over magnesium sulfate. After filtering and vacuum removal of solvent, the material was distilled, b.p. 116° (1 mm) to give 80% yield; nmr (carbon tetrachloride): δ 0.95 and 1.1 [2d, J = 8 Hz, 3, CHC*H*$_3$ (*cis* and *trans* arising from hindered rotation)], 1.6 (broad s, 3, =C-C*H*$_3$), 1.2-1.95 (m, exclusive of C-C*H*$_3$ absorption, 4 and 5 cyclohexenyl protons), 1.9-2.2 (m, 3, 3 and 6-cyclohexenyl protons), 2.90, 2.96 (2s, 3, *cis* and *trans* NC*H*$_3$), 4.00, 4.02 (2s, 2, *cis* and *trans* ClC*H*$_2$).

Anal. Calcd. for $C_{11}H_{18}ClNO$: Cl, 16.44; N, 6.49. Found: Cl, 16.50; N, 6.76.

3-Chloro-1-methyl-2(1*H*)quinolinone (**1a**).

2-Chloro-*N*-methylacetanilide (18.3 g., 0.1 mole), dissolved in 300 ml. of methylene chloride, was added at 0-5° to a solution of Vilsmeier reagent prepared from phosphoryl chloride (28 ml., 0.3 mole) and 82.5 ml. of dry DMF contained in 200 ml. of methylene chloride. After addition, the stirred mixture was allowed to warm to room temperature, then heated at reflux for three hours. After cooling, the stirred reaction mixture was treated with a stream of 400 ml. of 10 percent sodium carbonate solution. The two liquid phases were allowed to separate, and the methylene chloride solution washed once again with water. After phase

separation the organic layer was dried over magnesium sulfate. After filtering and vacuum removal of solvent, 8.8 g. of **1a** was obtained.

Freshly distilled *N*-(1,2-dichloroethenyl)-*N*-methylaniline (14) (25 g., 0.124 mole) possibly still containing unreacted 2,2-dichloro-*N*-methylacetanilide, was added in methylene chloride to a previously made slurry of 0.25 mole of Arnold reagent (0.25 mole of phosgene and 65 ml. of DMF) in 300 ml. of methylene chloride. There was no exotherm. The material was heated at reflux for 6 hours, then washed using the usual 10% aqueous sodium carbonate solution (300 ml.). A total of 7.0 g. of **1a** or 32% yield was obtained on purification.

3,6-Dichloro-1-ethyl-2(1*H*)quinolinone (**1c**).

3-Chloro-1-ethyl-2(1*H*)quinolinone (**1b**) (3 g.) was placed in excess sulfuryl chloride (20 ml.) and permitted to stand overnight. Comparison of sequential nmr's showed by the intensity of the changing =CH singlets when complete reaction had taken place. The sulfuryl chloride was removed under vacuum and the residue recrystallized from acetonitrile to give 2.1 g. of **1c**.

3-Chloro-1,7-dimethyl-2(1*H*)quinolinone (**1d**).

Phosphorus oxychloride (20 g., 0.13 mole) in 100 ml. of methylene chloride was added dropwise to 33 ml. of DMF contained in 200 ml. of the same solvent. The Vilsmeier reagent was allowed to form over one-half hour, then 8.4 g. of 2-chloro-*N*-methylaceto-*m*-toluidide in 100 ml. of methylene chloride added at 5°. The reaction mixture was then heated at reflux for four hours, cooled and 200 ml. of 10% sodium carbonate added. The organic layer was separated, dried and vacuum treated to give 7.0 g. of solid. The material was recrystallized from pyridine to give 3.8 g.

3-Chloro-6-methoxy-1-methyl-2(1*H*)quinolinone (**1f**).

The Vilsmeier reagent was prepared from 47.5 g. (0.31 mole) of phosphoryl chloride and 78 ml. of DMF in 400 ml. of methylene chloride. *N*-Methyl-2-chloro aceto-*p*-anisidine (21.3 g., 0.1 mole) in the same solvent was added to this reagent and then the whole heated at reflux for four hours. After cooling, and treatment with 400 ml. of 10% sodium carbonate in the fashion described above, the residue, after 2 recrystallizations from 2-propanol, gave 2.5 g. of **3f**.

1-Methyl-3-phenyl-2(1*H*)quinolinone (**1g**).

N-Methylphenylacetanilide (22.5 g., 0.1 mole) was reacted with Vilsmeier reagent (0.3 mole) in 300 ml. of methylene chloride, identical in procedure to **1a**. Recrystallization of crude product from 2-propanol gave 11.2 g; ms: [m/e (intensity)] 235 (100), molecular ion, 207 (3.5) molecular ion -CO.

3-Methoxy-1-methyl-2(1*H*)quinolinone (**1h**).

To 76 ml. of DMF in 200 ml. of methylene chloride at 10° was added phosphoryl chloride (46 g., 0.3 mole) dropwise. After addition and further stirring at this temperature for one-half hour, the solution was mixed with 2-methoxy-*N*-methylacetanilide (16 g., 0.09 mole) in 100 ml. of dichloromethane and heated at reflux for four hours. Neutralization of the cooled contents was achieved with 200 ml. of 10% sodium carbonate solution followed by addition of 40 g. of solid sodium carbonate to the stirred mixture. The organic layer was separated, solvent removed under vacuum to give an oil which partially solidified. Recrystallization from ethyl acetate, followed by carbon tetrachloride gave 1.0 g. of **1h**. The reaction was carried out again employing 10.5 g. (0.058 mole) of 2-methoxy-*N*-methylacetanilide. Examination of the crude residue after neutralization and solvent removal revealed from the nmr that the mixture consisted of 16% **1h** and 84% 3-chloro-2-methoxy-*N*-methylacrylanilide. The crude material was distilled through a six inch vigreux column at 113-130° (0.08 mm) to give 8.4 g. of an oil. This material was redistilled at the same temperature to give 7.0 g. of pure 3-chloro-2-methoxy-*N*-methylacrylanilide; ir (film): 6.0 (C=O); nmr (deuteriochloroform): δ 3.4, 3.6 (2 singlets, 6, CH_3O and NCH_3), 6.1 (s, 1, =*CH*Cl), 7.2-7.6 (m's, 5, Ar*H*).

Anal. Calcd. for $C_{11}H_{12}ClNO$: C, 58.54; H, 5.36; Cl, 15.71; N, 6.21. Found: C, 58.51; H, 5.37; Cl, 15.62; N, 6.23.

1-Methyl-3-methylthio-2(1*H*)quinolinone (**1i**).

To 78 ml. of DMF in 400 ml. of methylene chloride was added 31 g. (0.31 mole) of gaseous phosgene. After the Arnold reagent had formed, 19.5 g. of *N*-methyl-2-(methylthio)acetanilide (0.1 mole) was added in methylene chloride. The mixture was heated at reflux for five hours, cooled, then treated with 300 ml. of 10% sodium carbonate solution. After a further water wash, the organic layer was dried over magnesium sulfate, then vacuum treated to remove solvent. The residual red oil solidified on standing while recrystallization from 2-propanol gave 4.6 g.

4-Chloro-1-methyl-3-phenoxy-3,4-dihydro-2(1*H*)quinolinone.

N-Methyl-2-phenoxyacetanilide (24.1 g., 0.1 mole) in 150 ml. of methylene chloride was added to a solution of Vilsmeier reagent prepared by a half-hour reflux of 200 ml. of methylene chloride, 46 g. of phosphoryl chloride (0.3 mole) and 76 ml. of DMF. The mixture was heated at reflux for four hours, then treated with 300 ml. of 10% sodium carbonate solution. After a further water wash, the organic layer was dried over magnesium sulfate, then vacuum treated to remove solvent. The residue was recrystallized from 2-propanol to give 2.9 g. (10% yield), m.p. 100-101°; ir (carbon tetrachloride): 6.0 (C=O); uv (ethanol): $<$ 300 mμ (ε max $<$2000); nmr (deuteriochloroform): δ 6.42 and 6.60 (2 doublets, J = 0.5 Hz, 2, 3H, 4H).

Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.77; Cl, 12.32; N, 4.87. Found: C, 66.76; H, 12.28; H, 4.87.

3-Chloro-1-methyl-5,6,7,8-tetrahydro-2(1*H*)quinolinone (**2a**).

To 78 ml. of dimethylformamide (DMF) at 10° was added 47.5 g. (0.31 mole) of phosphoryl chloride. After allowing the Vilsmeier reagent to form over one-half hour, 18.8 g. (0.1 mole) of 2-chloro-*N*-methyl-*N*-(1-cyclohexen-1-yl)acetamide, in 300 ml. of methylene chloride was added at 10°. The reaction mixture was then heated at reflux for 4 hours, cooled, then 300 ml. of 10% sodium carbonate added. The organic layer was separated and dried over magnesium sulfate. After filtration and vacuum removal of solvent, the partially solidified residue was recrystallized from carbon tetrachloride to give 2.1 g.

3-Chloro-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)quinolinone (**2c**).

N-Phenylcyclohexylidene amine prepared from aniline and cyclohexanone was reacted with an equimolar amount of chloracetyl chloride in refluxing toluene to give 2-chloro-*N*-(1-cyclohexen-1-yl)acetanilide. This amide (24.9 g., 0.1 mole) was reacted in methylene chloride with the Vilsmeier reagent as described for **2a**. After refluxing for four hours, the mixture was hydrolyzed with aqueous sodium carbonate, and after drying and solvent removal, gave 23.9 g. of residue. Trituration by ether gave crystals, which upon recrystallization from 2-propanol gave 2.3 g. of **2c**; nmr (deuteriochloroform): δ 1.65 (m, 4H, 6- and 7-H), 2.05 and 2.5 (2m, 4H, 5- and 8-H), 7.05-7.6 (m's, 6H, Ar*H* and 4-H).

3,8-Dichloro-1-methyl-5,6,7,8-tetrahydro-2(1*H*)quinolinone (**2d**).

To 35.5 ml. of DMF in 300 ml. of methylene chloride at 15° was added 21.5 g. (0.14 mole) phosphoryl chloride. After stirring

at 15-20° for one-half hour, 9.2 g. (0.0415 mole) of *N*-(6-chloro-1-cyclohexen-1-yl)-*N*-methyl-2-chloracetamide in 50 ml. of methylene chloride was added. The mixture was refluxed for 4 hours, then allowed to cool and 200 ml. of 10% sodium carbonate added. To complete the neutralization 5 g. of additional sodium carbonate was added. After separating the organic layer, the solvent was removed under vacuum, leaving 4.5 g. of oily residue which solidified. Nmr showed predominantly product, which was recrystallized from ethyl acetate to give 2.2 g. from the first crop with 1.0 g. of additional **2d** collected as a second crop.

3-Chloro-1,4a-dimethyl-4a,5,6,7-tetrahydro-2(1*H*)quinolinone (**3a**).

The title material was prepared from either 2-chloro-*N*-(2-methyl-1-cyclohexen-1-yl)-*N*-methylacetamide, or 2-chloro-*N*-(6-methyl-1-cyclohexen-1-yl)-*N*-methylacetamide. The Arnold reagent (0.24 mole) was made up in 300 ml. of methylene chloride as described in **1i**, then 15 g. of amide was added, contained in 100 ml. of methylene chloride. There was no exotherm. The mixture was refluxed four hours, 300 ml. of 10 percent sodium carbonate added, and the organic layer separated. The solvent was removed and the residue distilled; **3a** was collected, b.p. 122° (0.05 mm). Material **3a** was also obtained by reacting three molar equivalents Vilsmeier reagent (DMF-phosphoryl chloride) with one molar equivalent of 2-chloro-*N*-(6-methyl-1-cyclohexen-1-yl)-*N*-methylacetamide (34 g., 0.169 mole). After the usual workup and distillation 10.1 g. of **3a** was collected, b.p. 122-134° (0.1 mm). On standing oil solidified, with recrystallization from cyclohexane.

3-Chloro-1,4a,8-trimethyl-4a,5,6,7-tetrahydro-2(1*H*)quinolinone (**3b**).

To 126 ml. of DMF in 300 ml. of methylene chloride was added 50 g. (0.5 mole) of phosgene at 10°. After stirring one-half hour, 35 g. (0.162 mole) of 2-chloro-*N*-(2,6-dimethyl-1-cyclohexen-1-yl)-*N*-methylacetamide in 50 ml. of methylene chloride was added dropwise. There was no exotherm. The mixture was then heated at reflux for six hours, with the color changing from orange to dark red. After standing overnight, 400 ml. of 10% sodium carbonate added, the organic phase separated, and the solvent removed vacuum, leaving a dark oily residue. This material was distilled to give **3b**.

REFERENCES AND NOTES

(1) Part V, J. P. Chupp, D. J. Dahm, K. L. Leschinsky, *J. Heterocyclic Chem.*, 12, 485 (1975).

(2) Presented at the 4th Biennial Rocky Mountain Regional Meeting of the American Chemical Society, Boulder, Co., June 5-7, 1978.

(3) W. Seshadri, *J. Sci. Ind. Res.*, 32, 128 (1973). See also by the same author, the lead article in over 18 publications on reactions of Vilsmeier reagent, *Ind. J. Chem.*, 662 (1969).

(4) H. G. Viehe and Z. Janousek, *Angew. Chem., Int. Ed. Engl.*, 12, 806 (1973).

(5) Z. Janousek, "The Chemistry of Phosgene Immonium Salts", a PhD dissertation, Catholic University of Louvain, Belgium 1972.

(6) R. G. Crenshaw and R. A. Partyka, *J. Heterocyclic Chem.*, 7, 871 (1970).

(7) For the lead paper in a series of over thirty publications on "Synthetic Reactions of Dimethylformamide", see Z. Arnold and A. Holy, *Collect Czech. Chem. Commun.*, 30, 47 (1965).

(8) Atta-ur-Rahman, A. Basha, N. Waheed, S. Ahmed, *Tetrahedron Letters*, 219 (1976).

(9) F. Schneierle, H. Reinhard, N. Dieter, E. Lippacher and D. Von Henning, *Ann. Chem.*, 715, 90 (1968).

(10) M. R. Chandramohan, M. S. Sardessai, S. R. Shah and S. Seshadri, *Indian J. Chem.*, 7, 1006 (1969).

(11) Little distinction was found here between the Vilsmeier reagent (from DMF and phosphoryl chloride) and the similar reagent from DMF and phosgene (often referred to as the Arnold reagent). Yields were comparable in all cases where both reagents were used; the advantages of facile neutralization and workup when the latter reagent was used is at least partially offset by the precautions necessary when working with toxic phosgene.

(12) T. Kaufmann and J. Schulz, *Chem. Ber.*, 99, 1837 (1966).

(13) H. Hubner, *ibid.*, 41, 483 (1908); *Beilstein*, 21, 348.

(14) A. J. Speziale and L. R. Smith, *J. Am. Chem. Soc.*, 84, 1868 (1962).

(15) G. H. Alt and J. P. Chupp, *Tetrahedron Letters*, 3155 (1970).

(16) J. P. Chupp, *J. Heterocyclic Chem.*, 8, 557 (1971); *ibid.*, 565 (1971).

(17) J. P. Chupp and E. Weiss, *J. Org. Chem.*, 33, 2357 (1968).

(18) For further details on preparations of enamides see U. S. Patent 3,574,746 to Monsanto Co., 1971.

(19) H. Weingarten, J. P. Chupp and W. A. White, *J. Org. Chem.*, 32, 3246 (1967).