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The Chemistry of Cyclic Enaminoketones. III. Synthesis of Bi- and Tricyclic Enaminoketones from Enamine Esters and Nitriles (1,2)

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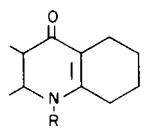
The cyclization of enamines derived from β-aminoesters and β-aminonitriles into bi- and tricyclic enaminoketones (**6**,**9**,**13** and **24**) has been investigated. The enamines derived from aminonitriles cyclize smoothly with magnesium perchlorate in benzene or toluene, whereas the enamines derived from aminoesters cyclize spontaneously during their formation. The scope and limitation of this process is discussed.

In a program aimed at evaluating the individual behavior (3) of cisoid (**1**) and transoid (**2**) cyclic enaminoketones and determining their utility as starting materials for otherwise difficulty accessible systems (4), it was initially necessary to devise synthetic methods to obtain a variety of these substances. This report is concerned with improved and novel approaches to the cisoid systems (**1**) whereas a future report will deal with studies in obtaining the transoid enaminoketones (**2**).



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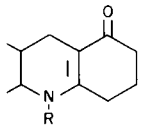

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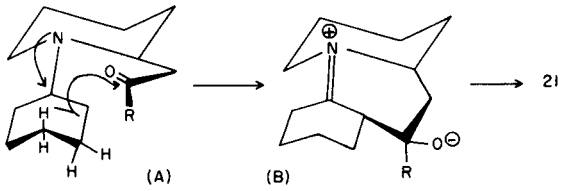
Systems of the type **1** have been reported by Bohlmann (5) arising from the mercuric acetate oxidation of β-aminoketones and cyclization of enaminoesters [**7** and **10** (n=2)] producing bi- and tricyclic enaminoketones, [**6** and **9** (n=2)] (6). The latter method (heating the enamines in ethylene glycol) produces mainly different products (6,7). When **12** was heated in ethylene glycol the major product was found to be the unsaturated amide, (**14**) rather than the expected enaminoketone (**13**) (6). Further side reactions have also been reported (8) when the enamine (**15**) was heated in ethylene glycol to give a comparable mixture of the "normal" (**16**) and "abnormal" (**17**) products. The preparation of tetracyclic enaminoketones (**3**) was recently reported (9) to proceed in fair-to-good yield in a single step from the tetrahydroisoquinoline esters (**5**) and cyclic ketones in refluxing toluene. It was pointed out in this paper that ethylene glycol was not necessary to effect cyclization of the enamine (**4**); in fact its presence was detrimental. The ease with which **5** formed the enamine and the cyclized product (**3**) was not observed when the aminoester (**8**) was similarly treated. The conversion to the enamine (**7**) was in excess of 80% yet the cyclized product (**6**) was obtained in only 35% yield along with the bicyclic lactam (**6a**) and the starting enamine. These results are in agreement with those reported by Horii, *et al.* (6). Furthermore, in order to obtain the pure bicyclic enaminoketone (**6**) tedious chromatographic separations were necessary.

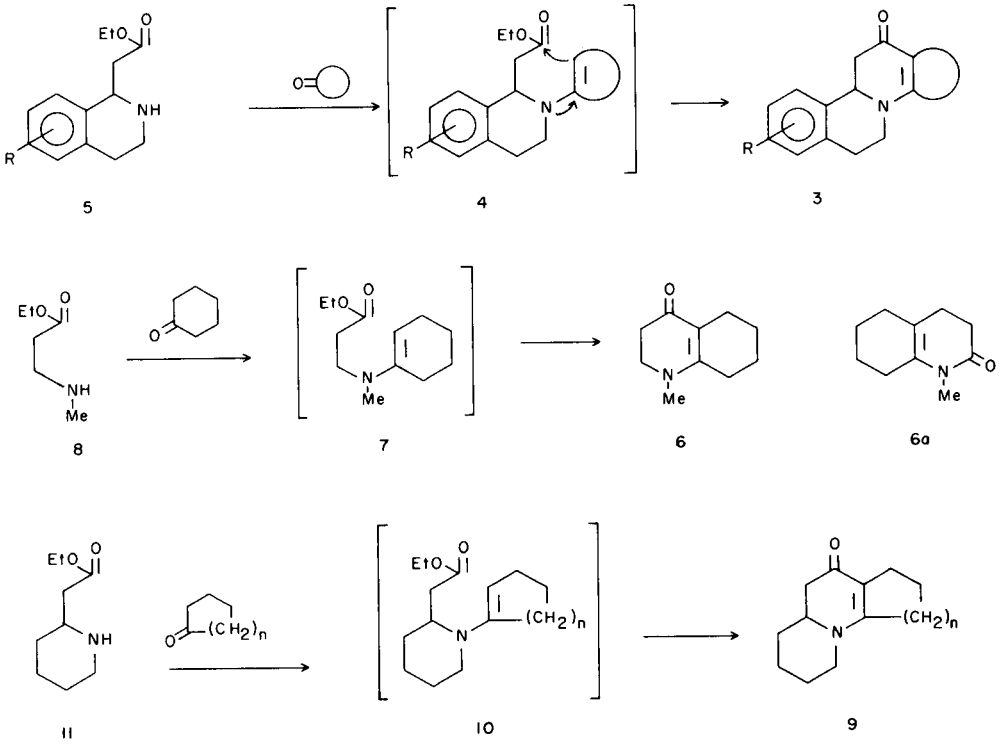
Examination of ethyl 2-piperidineacetate (**11**) as a suitable precursor to tricyclic enaminoketones (**9**) again proved to be fruitful. A toluene solution of the piperidine ester and cyclohexanone produced, after 48 hours of azeotropic water removal, 67% of **9** (n=2). There was no detectable evidence of any other product. The reaction was followed by removing samples from the

refluxing toluene solution and noting the increasing absorption of **9** (n=2) in the ultraviolet (218 mμ in toluene). A previous report (6c) described the identical reaction in the absence of solvent to form the "enamine" which was then heated at 180-200° to cyclize to **9** (n=2). The facile cyclization of the piperidine ester with other cyclic ketones produced tricyclic enaminoketones (**9**) containing five, seven, and eight membered fused rings (Table I).

In order to gain some insight into the factors affecting cyclizations of enaminoesters, a study was undertaken to determine the role of the leaving group. For this study the phenyl (**18**, X=OPh) and thiolic (**18**, X=SPh) esters were prepared and treated with cyclohexanone. The rate of formation of the enaminoketone (**9**) (n=2), was measured spectroscopically as a function of the absorbance of the N-C=C-C=O chromophore. The results (Figure 1) clearly indicate that the cyclization is highly dependent upon the nature of the leaving group (10). The thiophenyl ester could not be evaluated since it underwent polyamide formation rather extensively even in the early stages of the study. The relative rates for the formation of **9** (n=2) from the phenyl ester and the ethyl ester was approximately 150:1. The phenyl ester gave an 80% yield of the enaminoketone in refluxing toluene after 3 hours. These results are in agreement with the reaction of ethyl and phenyl esters with ammonia which showed that the phenyl ester is approximately 4 x 10^3 faster than the ethyl ester (11). The nature of this ring closure can be envisioned as a nucleophilic attack by the C=C bond of the enamine (**19**) to give the adduct (**20**) which then leads to loss of X^- to give the C-protonated enaminoketone (**21**). This process is completely analogous to the aminolysis of esters (10). The smaller difference in cyclization rates between the ethyl and phenyl esters (**18**) and that observed by aminolysis is accounted for by steric interaction of the phenyl group leading to **20**. Examination of molecular models confirm this view, namely that the attack of the C=C on the carbonyl portion of the ester is retarded considerably when R=phenyl due to serious non-bonded interactions with the cyclohexene ring (A). Thus the phenyl ester is attacked more slowly than the ethyl ester accounting for only the 150:1 rate ratio. The rate of loss of the ethoxy or the phenoxy group after the adduct (B) is formed would not be expected to be very different than that observed in the aminolysis of these esters. In the latter case where small nucleophiles (*i.e.*, ammonia) are involved, hinderance to carbonyl approach is probably much less significant.

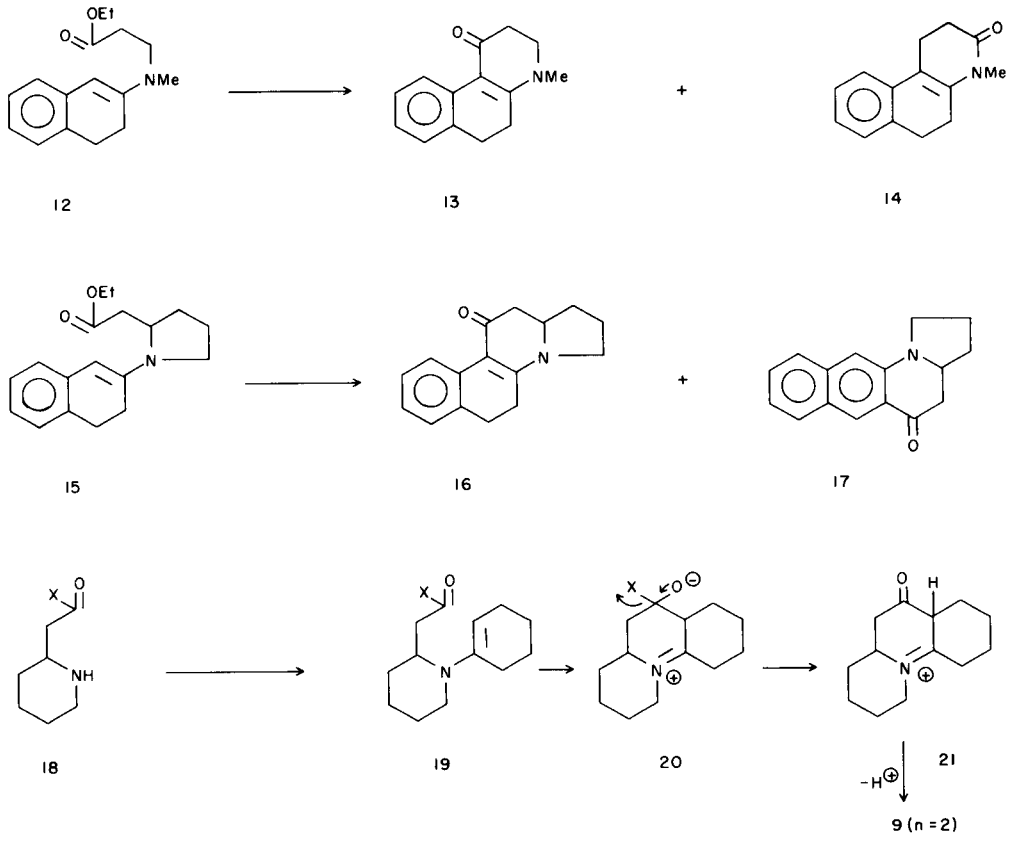


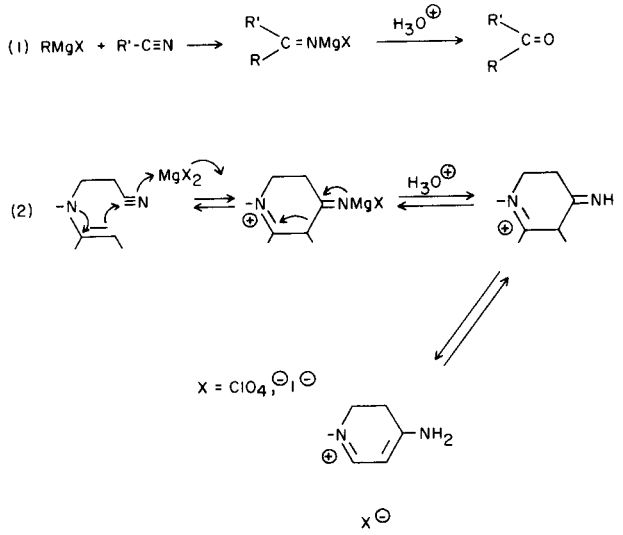
A search for an improved method for obtaining enaminoketones, particularly bicyclic systems (**6**), led to



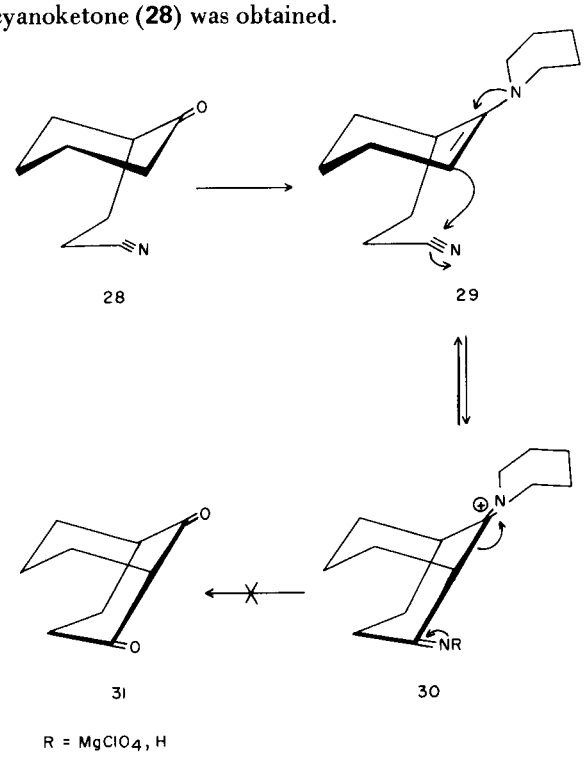
the investigation of β-aminonitriles (**22**) (12) in place of the β-aminoesters (**8**). If the ring closure mechanism as stated above is valid, then the nitrile function should lead to the formation of amino dihydropyridinium salts (**24**). The latter could be expected to be a suitable precursor to bicyclic enaminoketones (**25**). The enamines (**23**) derived from β-aminopropionitriles (**22**) were readily obtained by azeotropic water removal and were characterized by infrared and NMR techniques (Table II). They slowly deteriorated on prolonged standing when exposed to air and were therefore utilized as soon as possible. When a benzene solution of the enamine, (**23**) (R=Me, n=2) containing 1.1 equivalent of magnesium perchlorate ("Anhydrone")* was warmed to 50-70° for 2.5 hours, the powdery magnesium salt became an amorphous mass. After removal of the benzene and treatment with aqueous ammonium chloride solution, a quantative yield of **24** (R=Me, n=2) was obtained. The product exhibited an absorption at 350 mμ and infrared bands at 2.8, 2.9 (NH_2) and 6.5 μ. The perchlorate salt was insufficiently soluble in the usual solvents to allow its NMR spectrum to be recorded. Alkaline hydrolysis of this aminoperchlorate produced a quantitative yield of the bicyclic enaminoketone (**25**) (R=Me, n=2) which was identical with **6** prepared earlier. A variety of cyclic ketones were employed and resulted in aminodihydropyridinium salts (Table III) in various yields. The bicyclic enaminoketones (**25**) were subsequently obtained by hydrolysis of **24** (Table IV). This technique, under more drastic conditions, has already been reported (13) for the isoquinoline nitrile (**26**) leading to the tetracyclic systems **27** and **3**.

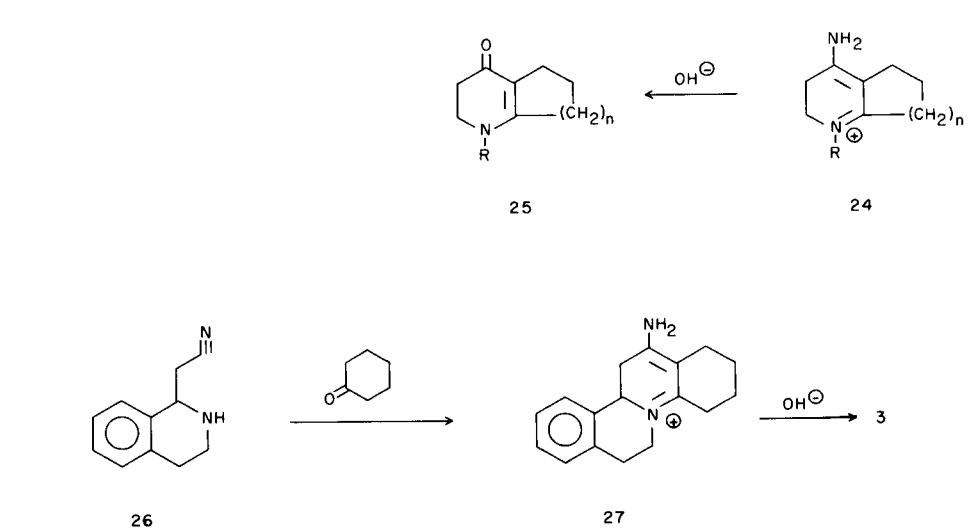
The role of the metal ion in this enamine-nitrile cyclization was studied to determine whether any specificity exists. It was found that anhydrous magnesium iodide performed as well as the corresponding perchlorate, however, its cost and hygroscopic nature were the main reasons for deferring any further studies. The role of the magnesium ion in this cyclization is somewhat analogous to the reaction of Grignard reagents and nitriles (eq. 1). The enamine double bond (eq. 2) displaces a π-bond from the nitrile group which in turn is sufficiently nucleophilic to displace the anion from the magnesium salt. The magnesium adduct, were it soluble in the reaction medium (benzene) could well undergo reversal to the enamine, but due to its insoluble nature remains intact. When the latter is hydrolyzed under mild conditions, the >=NH tautomerizes rapidly to the conjugated system.

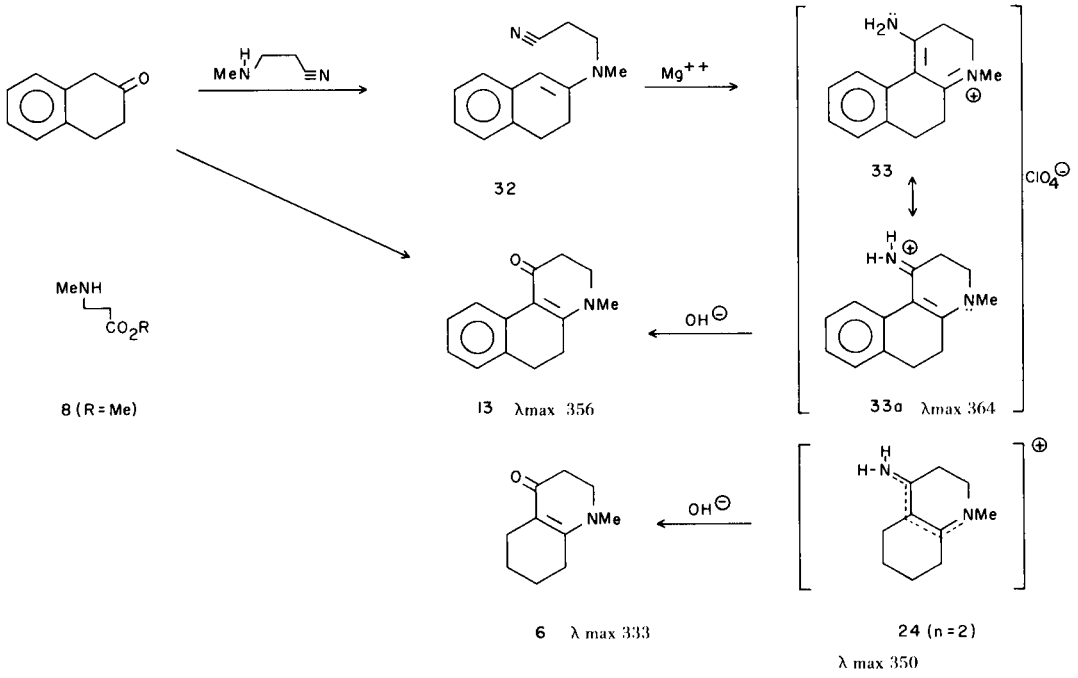




It is believed that this reaction is successful only when the >=NH group is readily convertible to an extended conjugated system. This is supported by the fact that the cyanoethyl cyclohexanone (**28**) when converted to its enamine (**29**) (13) gave only starting material after treatment with magnesium perchlorate in benzene. It is not known at this time whether the cyclization took place to give **30** (R=$MgClO_4$) and then, after decomposition of the amphorphous complex, the imino derivative,(**30**) (R=H) reverted rapidly to the starting enamine, since conjugation with the iminium group is not possible in the bicyclic molecule. None of the desired bicyclo[3.3.1]nonadione (**31**) could be detected, although 90% recovery of the cyanoketone (**28**) was obtained.







Attempts to employ silver, copper, and lithium perchlorate in the cyclization of enamine-nitriles, (**23**) did not produce any of the desired cyclic systems, (**24**) but only starting materials (enamines, cyclic ketones, and **22**).

In order to further extend the scope of this facile ring closure to other heterocyclic systems, the enamine (**32**) of β-tetralone was prepared and treated with magnesium perchlorate in toluene (95°) for 10 hours. The tricyclic amino perchlorate salt (**33**) was obtained pure in 50% yield, which upon hydrolysis quantitatively produced the benzo(*f*)quinolin-4-one, (**13**). The structures of **33** and **13** were totally consistent with all spectroscopic data.

It is of interest that Nelson, *et al.* (14) in attempting to prepare **13**, utilizing the β-methyl aminopropionic ester (**8**) and β-tetralone obtained, instead, mainly **14** and "a different substance in about 5% yield, m.p. 120.5-121.4° which has not been characterized". This 120° product could indeed have been **13**, the compound that Nelson, *et al.* had originally set out to prepare.

The ultraviolet spectrum of **33** when compared to its hydrolysis product (**13**) shows a Δ λ max of only 8 mμ, whereas comparison of the bicyclic aminoperchlorate salts, (**24**) with its hydrolysis product shows Δ λ max of 17 mμ. Since it would be expected that the phenyl conjugation in **33** and **13** would cause their chromophore to shift to the red, the smaller difference in these two compounds as compared to the bicyclic systems must be due to the famed "steric inhibition of resonance". The amino group cannot lie coplanar to the π-bonds (**33a**) due to interaction with the *peri*-hydrogen in the aromatic ring, thus resulting in partial destruction of the delocalization energy in **33**. This effect is absent in the bicyclic systems **24** and **6** and therefore a greater difference in absorption is noted. In **13** the NMR spectrum reveals that the carbonyl oxygen is in close proximity to the *peri*-hydrogen resulting in a significant downfield shift of this proton (1.75 τ, doublet). This effect of the carbonyl group in analogous compounds (*i.e.*, **16**) has also been noted (8).

Further studies on enamines containing a nitrile group in a variety of structures and their cyclizations using magnesium ion are in progress.

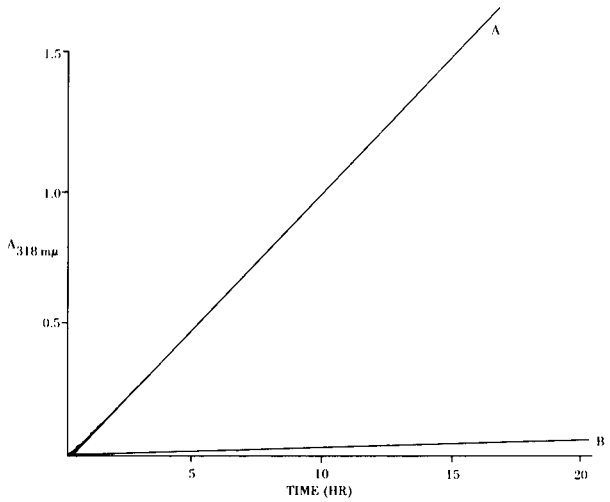
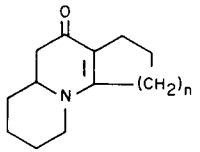


FIGURE 1

A- Rate of formation of **9** (n=2) from phenyl ester, **18** (X=OPh) in toluene at 80°
B- Rate of formation of **9** (n=2) from ethyl ester **18** (X=OEt) in toluene at 80°

TABLE I

Cycloalkeno[*h*]quinolizidin-6-ones, **9**

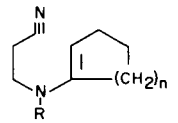


n	M.P.° C (a)	Bp° (mm Hg)	λ (c) (μ)	λ max (EtOH)	% Yield	Formula	Analyses, Found (b)		
							C	H	N
1	67-68	150-155 (0.8)	6.08, 6.32	333 (18,000)	61	$C_{12}H_{17}NO$	75.18	8.78	7.25
2	77-78	170-180 (1)	6.10, 6.48	336 (14,000)	67	$C_{13}H_{19}NO$	76.40	9.49	6.84
3	59	165-175 (0.5)	6.13, 6.54	340 (16,300)	60	$C_{14}H_{21}NO$	76.62	9.69	6.15
4	83-84	178-185 (0.65)	6.15, 6.48	342 (16,525)	61	$C_{15}H_{23}NO$	77.03	9.97	6.17

(a) Recrystallized from *n*-hexane. (b) Agrees well with calculated values. (c) Taken in carbon tetrachloride.

TABLE II

2-(*N*-Alkyl-*N*-cycloalkenyl)propionitriles, **23**

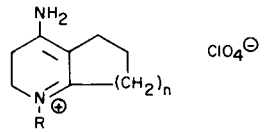


R	n	% Yield	Bp° (mm Hg)	λ (μ)	τ ($CDCl_3$)	
CH_3	1	93	85 (0.1)	4.42, 6.13	5.81, (a)	7.33 (b)
CH_3	2	81	115 (0.1)	4.42, 6.08	5.52, (a)	7.41 (b)
CH_3	3	25	110 (0.1)	4.41, 6.09	5.21, (a)	7.49 (b)
CH_3	4	13	115 (0.1)	4.40, 6.10	5.56, (a)	7.38 (b)
$-(CH_2)_2NEt_2$	1	60	119 (0.075)	4.40, 6.15	5.85, (a)	-------
$-(CH_2)_3NEt_2$	1	74	134 (0.2)	4.45, 6.15	5.84, (a)	-------
$-(CH_2)_3NEt_2$	2	37	129 (0.1)	4.44, 6.13	5.45, (a)	-------
$-(CH_2)_2NEt_2$	2	56	137 (0.4)	4.40, 6.10	5.45, (a)	-------

(a) Vinyl signal, diffuse triplet. (b) *N*-Methyl singlet.

TABLE III

N-Methyl-4-amino-5,6-dihydro-2,3-cycloalkanopyridinium Perchlorates, **24**

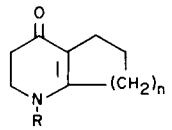


R	n	M.P.° C	% Yield	λ max (EtOH) (b) mμ	λ (a) (μ)	Formula	Analyses, Found (c)		
							C	H	N
CH_3	1	131-132	74	345	2.8, 2.9, 6.5	$C_9H_{15}ClO_4N_2$	43.30	6.14	11.04
CH_3	2	131-132	84	350	2.8, 2.9, 6.4	$C_{10}H_{17}ClO_4N_2$	45.26	6.39	10.64
CH_3	3	148-149	70	350	2.8, 2.9, 6.6	$C_{11}H_{19}ClO_4N_2$	47.60	6.83	10.16
CH_3	4	165-166	35	353	2.8, 2.9, 6.6	$C_{12}H_{21}ClO_4N_2$	49.48	7.41	9.70
$-(CH_2)_2N(C_2H_5)_2$	2	oil	54	351	2.9, 3.0, 6.0-6.2	$C_{15}H_{28}ClO_4N_3$	51.25	7.99	12.26
$-(CH_2)_2N(C_2H_5)_2$	1	oil	50	345	2.9, 3.0, 6.0-6.2	$C_{14}H_{26}ClO_4N_3$	49.66	7.67	12.36

(a) Nujol. (b) Extinction coefficients for all compounds 14-16,000. (c) Agrees well with calculated values.

TABLE IV

N-Alkyl-1,2,3,4-tetrahydro-4-oxo-5,6-cycloalkanopyridine, **25**



R	n	% Yield	λ max (EtOH) (ε)	λ (a) (μ)	Picrate, M.P.°	Analyses, Found (c)		
						C	H	N
CH_3	1	92	333 (15,600)	6.17, 6.44	149-150	47.50 (b)	4.38	14.78
CH_3	2	80	336 (14,350)	6.10, 6.34	156	48.70 (b)	4.46	13.89
CH_3	3	82	340 (14,000)	6.18, 6.44	119-120	50.04 (b)	5.05	13.76
CH_3	4	97	342 (14,200)	6.12, 6.38	131-132	51.37 (b)	5.38	13.02
$(CH_2)_2N(C_2H_5)_2$	2	75	338 (11,000)	6.05, 6.12	146-150 (0.2 mm)	72.12	10.68	10.92
$(CH_2)_2N(C_2H_5)_2$	1	85	333 (12,000)	6.05, 6.15	160-170 (0.4 mm)	71.21	10.38	11.78

(a) Neat. (b) Picrate salts. (c) Agrees satisfactorily with calculated values.

EXPERIMENTAL (15)

Piperidine-2-acetic Acid (**18**, R=OH).

A solution of 15 g. (8.8 mmole) of the ethyl ester, (17) **11** in 100 ml. water containing 20 g. of barium hydroxide was refluxed for 1.5 hours and cooled. Dry ice was added and the precipitated barium carbonate removed by filtration. The aqueous solution was concentrated to 20 ml. and the precipitated amino acid (12.5 g.) collected and recrystallized with absolute alcohol, m.p. 226° (lit. (17) 214°).

Phenyl 2-Piperidylacetate (**18**, R=PhO).

To a solution of reagent quality acetyl chloride (100 ml.) containing 9 g. of phosphorus pentachloride, previously cooled to 0-3° was added, all at once, 5 g. of the amino acid, (**18**) (R=OH). The solution was stirred for 4 hours after which the product was collected by filtration. After washing repeatedly with petroleum ether, the acid chloride (18) was utilized immediately, since it could not be purified further. The acid chloride, (5 g.) obtained in this manner, was heated in 20 g. of freshly distilled phenol at 100-125° for 20 minutes. Upon cooling and addition of 100 ml. of anhydrous ether, the phenyl ester hydrochloride was obtained as a crystalline material, 6.6 g. (84%), m.p. 228° (EtOH), IR (Fluorolube) 5.8 μ;

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.04; N, 5.47. Found: C, 60.94; H, 7.01; N, 5.36.

The free base, was obtained from its hydrochloride salt by extraction, (methylene chloride) of an aqueous solution containing 3 equivalents of sodium bicarbonate. After concentration of the methylene chloride solution, the phenyl ester was obtained as a viscous oil which did not crystallize. IR (neat) 5.70 μ; NMR (deuteriochloroform); 2.5-3.2 τ (phenyl multiplet, 5H); 8.05 τ (NH, singlet exchangeble with deuterium oxide).

Phenyl 2-Piperidylthioacetate (**18**, R=SPh).

The piperidine acetyl chloride, prepared as above, was treated with 100 ml. of freshly distilled thiophenol in a flask protected from moisture and air. The mixture, under nitrogen, was heated for 20 minutes at 100° (evolution of hydrogen chloride had ceased during this time) and cooled with stirring. The addition of 100 ml. of anhydrous ether precipitated the thiophenyl ester hydrochloride (8 g., 85%), m.p. 179-180° (methanol, -15°), IR (fluorolube) 5.88 μ.

Anal. Calcd. for $C_{13}H_{18}ClNOS$: C, 57.45; H, 6.68; N, 5.16. Found: C, 57.64; H, 6.76; N, 4.96.

The free thioester polymerizes readily on warming in ethanol, but not in acetonitrile (appearance of polyamide band at 6.10 μ).

2-(*N*-Alkyl-*N*-cycloalkenyl)aminopropionitriles (**23**). Typical Procedure.

A mixture of 2-(*N*-alkyl)aminopropionitriles (0.22 mole), cycloalkanone (0.44 mole in case of cyclohexanone and cyclopentanone, and 0.24 mole in case of cycloheptanone and cyclooctanone) and toluene (120 ml.) was refluxed in the presence of 0.01 eq. toluenesulfonic acid for 24-36 hours or until no further water was azeotropically removed. Evaporation of the solvent and distillation of the residue produced the enamines in variable yields (Table II). No attempt to obtain analytical data was made in view of the tendency of these materials to hydrolyze. Complete spectroscopic data is recorded in Table II.

N-Alkyl-4-amino-5,6-dihydro-2,3-cycloalkanopyridinium Perchlorates, (**24**).

A suspension of anhydrous powdered magnesium perchlorate (0.22 mole) in 30 ml. of dry benzene was treated with the enamine nitriles, (**23**) (0.20 mole) and the mixture heated with vigorous stirring to 55-80° for 2.5-4.5 hours.* The powdered magnesium salt slowly became brown and tacky during this period. The benzene solution was decanted from the solid mass and the latter washed twice with fresh benzene. The complex was then treated with 10% aqueous ammonium chloride and the precipitated solid (or oil) was taken up with methylene chloride and dried (sodium sulfate). After removal of the solvent, the resulting oil was triturated with ethyl acetate and solidified in all cases except where R=diethylaminoalkyl. The products were recrystallized from ethyl acetate-methanol. In the case of the oils "recrystallization" in the same manner was carried out and the precipitated oils were separated and dried *in vacuo* for 48 hours (Table III).

N-Alkyl-4-oxo-5,6-cycloalkano-1,2,3,4-tetrahydropyridine, (**25**).

A mixture of 200-300 mg. of aminopyridinium perchlorate salts (**24**) in 25 ml. (a 3:1 mixture of methanol-10% sodium hydroxide) was refluxed for 2.5 hours and the clear solution concentrated *in vacuo* to remove the alcohol. The aqueous solution was extracted with methylene chloride and the latter solution dried (sodium sulfate) and concentrated. The bicyclic enaminoketones were obtained as oils and characterized (Table IV).

Cycloalkeno[*h*]-6-oxoquinolizidines, (**9**).

A solution of 0.06 mole ethyl 2-piperidylacetate, 0.12 mole of cycloalkanone, 2 ml. of trifluoroacetic acid and 50 ml. of toluene was heated with azeotropic water removal of 48 hours in a nitrogen atmosphere. The toluene solution was washed with 5% sodium bicarbonate solution and then with water and dried (sodium sulfate). After removal of the toluene on a rotary evaporator, the viscous residue was distilled to afford the enaminoketones (**9**). The product crystallized on standing or after trituration with petroleum ether. Recrystallization of the products was accomplished using *n*-hexane (Table I).

β-[*N*-Methyl, *N*-(2,3-dihydronaphthenyl)] aminopropionitrile, (**32**).

A solution of 2.92 g. of β-tetralone, 1.85 g. of β-*N*-methylaminopropionitrile, and 35 ml. of toluene was heated with azeotropic water removal for 9.5 hours under nitrogen. The toluene was removed *in vacuo* and the residual oil [IR (neat): 4.42, 6.20 μ. λ max (EtOH), 305, 228, 212 mμ; NMR (deuteriochloroform τ): 2.90 (aromatic, 4H); 4.67 singlet (vinyl 1H); 7.18 singlet ($N\text{-}CH_3$, 3H)] used directly in the subsequent procedure.

1-Methyl-4-amino-2,3,9,10-tetrahydro-benzo[*f*]quinolinium Perchlorate, (**33**).

A solution of 1.0 g. of the above enamine in 25 ml. of dry toluene was treated with 1.25 g. of anhydrous magnesium perchlorate and heated, under nitrogen with efficient stirring for 10 hours at 95°*. The toluene was decanted away from the amorphous, tacky complex and the latter washed several times with petroleum ether. The complex was then decomposed with saturated ammonium chloride solution and the resulting solid collected on a filter, washed with water, and dried. The solid slowly turned dark green due to the presence of β-tetralone which is readily susceptible to air oxidation. However, recrystallization from methanol-ether retained the dark material and deposited the pure product (**33**) m.p. 247-248° dec.; IR (nujol): 2.87, 2.96, 6.08, 6.18, 6.53 μ; λ max (EtOH), 364 (11,200) 272 (12,130) 220 (11,680), yield, 890 mg (60%).

Anal. Calcd. for $C_{14}H_{17}ClN_2O_4$: C, 53.76; H, 5.44; N, 8.96; Cl, 11.36. Found: C, 53.60; H, 5.39; N, 8.99.

1-Methyl-4-keto-1,2,3,4,9,10-hexahydrobenzo[*f*]quinoline, (**13**).

The salt (**33**) was hydrolyzed by treating 386 mg. with 10 ml. of aqueous methanolic (1:3) sodium hydroxide (10%) and refluxing for 3 hours. After evaporation of the methanol, the addition of 25 ml. of water precipitated a solid, 262 mg. (95%), m.p. 94-96°. Recrystallization from ethyl acetate raised the m.p. to 120-120.5° (lit. (6c) 96-97°) IR (chloroform): 6.18, 6.27 and 6.50 μ; λ max (EtOH), mμ: 356 (10,500), 280 (15,320), 222 (10,800); NMR (deuteriochloroform, τ): 1.75 doublet, (1H); 2.90-3.0 (3H); 6.93 singlet (3H).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.84; H, 7.02; N, 6.60. Mol. Wt. (M/e = 213).

β(*N*-Alkyl)aminonitriles.

β-(*N*-Alkyl)aminonitriles were prepared according to the procedure of Whitmore, *et al.* (19).

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**CAUTIONARY NOTE: Although some 50 experiments utilizing magnesium perchlorate* ($Mg(ClO_4)_2$-$2H_2O$) *have been run without a mishap, we have experienced one violent explosion in which several people were injured. The reasons, we believe, for this unfortunate incident were due to the use of a heating mantle rather than an oil bath to heat the reaction, and a small stirrer without sufficient torque to keep the magnesium complex in suspension. In every case where an oil bath and high torque motor was employed, no difficulty was encountered.*

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