significant absorption above 260 mμ. For compound IV, λ_{max} 223 mμ (ε 37,880).

Metal Extractions.—For each extraction 20.00 ml. of a 6 *N* acid solution containing 200 p.p.m. of the metal as the nitrate or chloride was shaken for 5 min. on a mechanical shaker with 20.00 ml. of a solution of IIb (0.05 *M*), III (0.05 *M*), tri-*n*-butyl phosphate (0.1 *M*), or tri-*n*-octylphosphine oxide (0.1 *M*) in cyclohexane. Compound IV was used as a 0.05 *M* solution in chloroform as it was insoluble in cyclohexane. The phases were then separated, and the aqueous phase was analyzed for the metal by X-ray fluorescence. The results (Table II) are expressed as per cent metal salt extracted from the aqueous phase, using solutions extracted with cyclohexane alone as blanks.

Acknowledgments.—We are indebted to Mr. Leon A. Zengierski for capable technical assistance; to the members of our analytical and instrumental laboratories for their cooperation, and in particular to Mr. Anthony J. Iwaszko for the X-ray fluorescence analyses; and to Dr. Charles F. Baranauckas for his guidance and encouragement.

Azasteroids. V. The Direct Conversion of 1-(Carboethoxymethyl)-1,2,3,4-tetrahydroisoquinolines and Cyclic Ketones into Benzo[a]cycloalkano[f]quinolizinones. An Example of Enamine Acylation by an Ester Function[1,2]

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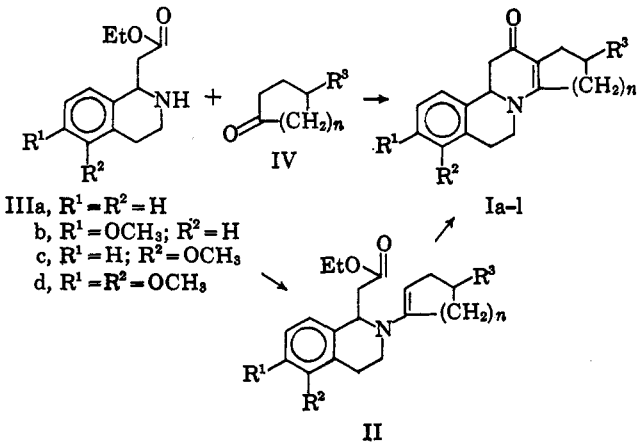
The intramolecular cyclization of N-(cycloalkenyl)-1-carbethoxymethyl-1,2,3,4-tetrahydroisoquinolines (II) in hot ethylene glycol has been re-examined and found not to require the latter solvent. The formation of benzo[a]cycloalkano[f]quinolizinones (I) is described under the conditions which are commonly expected to lead only to the enamines. The reaction proceeds with or without the use of acid catalysts, although the yields are higher and the reaction time shorter when they are employed. The perchlorate salts of these enamino ketones (I) were prepared and found to be O-protonated.

As part of a general program to synthesize totally azasteroids, various approaches to the construction of the steroidal skeleton have been considered.[5] In a recent communication,[6] a model for the 8- and 9-azasteroids was described employing as starting materials the tetracyclic enamino ketones (benzo[a]-cycloalkano[f]quinolizinones), Ie (R^1 = OCH_3; R^2 = R^3 = H; n = 1) and Ij (R^1 = H; R^2 = OCH_3; R^3 = OCH_2CH_2O–; n = 2). The former was considered to be a useful precursor to 8-azasteroids whereas the latter could provide a pathway to 9-azasteroids. Both of these starting compounds were prepared by condensing the appropriate tetrahydroisoquinoline esters (III) and cyclic ketones (IV) to give II according to the usual enamine procedures.[7] Replacement of the toluene solvent with ethylene glycol, and heating overnight at 170–180° gave I. The structure of Ie and Ij were supported by the infrared spectra which exhibited two strong bands in the region of 6.0–6.5 μ, typical of β-amino α,β-unsaturated ketones[8] and ultraviolet maxima in the 300–310-mμ region consistent with the N—C=C—C=O chromophore.[9] The position of the carbon–carbon double bond is established by the absence of any vinyl proton n.m.r. signal and the chemical shift of the lone proton adjacent to nitrogen and the phenyl group at τ 5.3.

Although these two compounds are considered extremely useful for further studies on azasteroids, the poor yields (Ie, 26%, and Ij, 18%) obtained by this method left much to be desired in view of the fact that many subsequent synthetic steps would be necessary before the final goal was reached. It was felt that a more detailed examination of the enamine cyclization in ethylene glycol was necessary before proceeding to seek out alternative procedures. Since the tetrahydroisoquinoline esters, IIIb and IIIc, were both difficult and costly to come by, studies were carried out using the readily available IIIa (*cf.* Experimental Section). Treatment of the latter with cyclopentanone in toluene with azeotropic removal of water gave the



(1) This study was supported by funds granted by the National Institutes of Health (GM-06248-06).

(2) Presented before the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965.

(3) On leave from the Institute of Organic Synthesis, Polish Academy of Sciences, Warsaw, Poland.

(4) Institute of Chemistry, "Alonso Barba," Madrid, Spain.

(5) A. I. Meyers, N. K. Ralhan, and J. Schneller, *J. Org. Chem.*, **28**, 2944 (1963); A. I. Meyers and N. K. Ralhan, *ibid.*, **28**, 2950 (1963); A. I. Meyers, N. K. Ralhan, B. J. Bertus, and K. Baburao, *J. Heterocyclic Chem.*, **1**, 13 (1964).

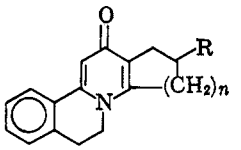
(6) A. I. Meyers, G. G. Munoz, W. Sobotka, and K. Baburao, *Tetrahedron Letters*, **No. 4**, 255 (1965).

(7) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(8) (a) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Franck, and D. J. Wallace, *ibid.*, **71**, 3337 (1949); (b) G. O. Dudek, *J. Org. Chem.*, **30**, 548 (1965).

(9) F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Reusche, *Ber.*, **94**, 1774 (1961); F. Bohlmann and O. Schmidt, *ibid.*, **97**, 1354 (1964).

corresponding enamine (II) which, after removal of the solvent, was heated to 170–180° in ethylene glycol for 12–15 hr. There was obtained, in addition to Ia and dark colored tars, a small quantity of a high-melting compound (260°) which did not exhibit the usual spectral properties of Ia (or Ie and Ij). The ultraviolet spectrum showed two maxima at 256 mμ (log ε 4.51) and 286 mμ (log ε 4.23), whereas the n.m.r. spectrum exhibited a sharp singlet in the vinyl proton region (τ 3.19). These data, coupled with the elemental analysis, are consistent with the 4-pyridone system, V. When IIIa was similarly treated with 4-methoxycyclohexanone, once again a high-melting product (205°) was isolated in addition to the enamino

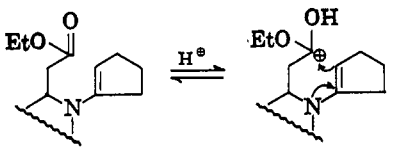


V, R = H; $n = 1$
VI, R = OCH_3; $n = 2$

ketone Id. The spectral properties of the former were very similar to V (λ_{max} 256 and 282 mμ, vinyl singlet at τ 3.21) and on this basis was also assigned the 4-pyridone structure, VI. The yields of V and VI were 4 and 7%, respectively. The formation of the 4-pyridones can readily be explained by considering the ease with which the benzylic proton can be oxidized. This is mainly due to the aromaticity of the pyridone system which provides the necessary driving force for the oxidation.

The large amount of tarry material always present after the high-temperature cyclization prompted the desire to utilize, if feasible, a purified enamine prior to cyclization. In previous experiments, enamines were assumed to be sufficiently pure for further use merely by evaporating the solvent and excess ketone *in vacuo*. This degree of purity was established by examining the viscous residue by infrared methods which clearly showed the enamine stretching frequency between 6.1 and 6.2 μ.[10] The azeotropic water removal was usually continued until the enamine band showed no further increase in intensity. When the ultraviolet spectrum of the crude enamine, II ($R^1 = R^2 = R^3 = H$; $n = 1$) was examined, there appeared a strong maximum at 310 mμ. This absorption is not typical of a simple enamine[10] moiety, but was reminiscent of the absorption exhibited by the enamino ketones, I. The addition of petroleum ether to the crude enamine caused the precipitation of a crystalline solid which was identical in every respect with Ia, obtained *via* the ethylene glycol procedure. The yield of Ia, precipitated from the enamine, was 25%. In another experiment, using the same quantities of IIIa and cyclopentanone and the same reaction time, the enamine residue was heated in ethylene glycol under the usual conditions. There were isolated Ia and V, in 18 and 5% yields, respectively. It is therefore reasonable to conclude that subsequent heating of the "enamines" in ethylene glycol does little or nothing to produce the tetracyclic enamino ketones and, in fact, may be detrimental to the process. Since there were no pyridones (V and VI) found by treating the isoquinoline esters and ketones in toluene, they are undoubtedly formed only during the high-temperature treatment in ethylene glycol. Thus, the adaptation of the procedure by Nelson, *et al.*,[11] wherein ethylene glycol was employed to cyclize "enamines" proved to be of little value for obtaining these compounds.

A variety of tetrahydroisoquinoline esters, IIIa–d, and cyclic ketones were subjected to similar treatment, *viz.*, refluxing toluene and azeotropic water removal for 5–7 days. The yields of I (Table I, per cent yield under A) ranged from excellent (Ib) to poor (Ih). The use of other solvents (dimethylformamide, dimethyl sulfoxide, benzene, and diglyme) proved to be of no significant advantage. The use of acid catalysts provided some encouraging results. *p*-Toluenesulfonic acid did increase the yields slightly and shorten the reaction time, but considerable amounts of unreacted enamine were always present. The n.m.r. spectrum of aliquots, removed during the heating periods, always exhibited a well-defined vinyl triplet (τ 5.08, $J = 7.5$ c.p.s.) of the enamine. When trifluoroacetic acid was employed in catalytic amounts, the yields were consistently good (Table I, per cent yield under B). The reaction time was 20–40 hr. The observed behavior in the presence of the acid catalyst is not unusual since the rate of enamine formation is known to be enhanced under these conditions. However, the cyclization process, unexpectedly, must also be favored by acid owing to the increased electrophilic character of the ester carbonyl by protonation (VII ⇌ VIII).



VII VIII

The use of an ester group as an acylating agent has only been reported in a few isolated cases,[9b,10,12] all of them being of the intramolecular type. The intermolecular process using ester carbonyls as acylating agents is still unknown although attempts have been made.[7] The possibility of a ketene intermediate derived from the ester function seems unlikely in view of the relatively mild conditions and acid catalyst employed.

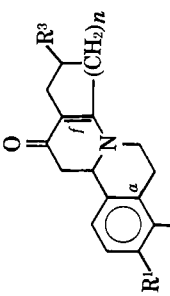
The perchlorate salts of Ia–l were prepared by usual methods and exhibited strong absorption in the 2.7–2.9-μ region which suggests O-protonation. However, the ultraviolet spectra were much more useful in determining the site of protonation. A comparison of the spectra of the free bases in ethanol and the perchlorates in the same solvent showed remarkably similar absorption (Table II). This can only be due to the similarity in the chromophores possessed by the free bases and the perchlorates (O=C—C=C—N̈< and HO—C=C—C=$\overset{\oplus}{N}$<), respectively. Protonation of

(10) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 96 (1963).

(11) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958). A subsequent report revealed that the "cyclization" of an enamine ester in ethylene glycol did not lead, as previously thought, to a cyclic enamino ketone: Z. Horii, C. Iwata, Y. Tamura, N. A. Nelson, and G. H. Rasmusson, *J. Org. Chem.*, **29**, 2768 (1964).

(12) Z. Horii, C. Iwata, I. Ninomiya, N. Inamura, M. Ito, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **12**, 1405 (1964).

TABLE I. BENZO[a]CYCLOALKANO[f]QUINOLIZINONES



Compd.	R¹	R²	R³	n	% yield[a] A	% yield[a] B	M.p., °C.[b]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Perchlorate m.p., °C.[c]
Ia	H	H	H	1	36	74	161–162	$C_{16}H_{17}NO$	80.30	7.16	5.85	80.60	7.24	5.78	188–189
Ib	H	H	H	2	93	80	173–174	$C_{17}H_{19}NO$	80.63	7.50	5.53	80.78	7.64	5.55	231–232
Ic	H	H	H	3	19	70	151–152	$C_{18}H_{21}NO$	80.89	7.86	5.29	81.03	8.02	5.29	236–238
Id	H	H	CH_3O	2	26	81	159–160	$C_{18}H_{21}NO_2$	76.40	7.43	4.95	76.30	7.26	4.90	186–187
Ie	CH_3O	H	H	1	21	70	185–187	$C_{17}H_{19}NO_2$	75.81	7.11	5.20	75.94	7.20	5.08	224–225
If	CH_3O	CH_3O	H	1	24	74	215–217	$C_{18}H_{21}NO_3$	72.24	7.05	4.68	72.14	7.23	4.45	117–119
Ig	CH_3O	CH_3O	H	2	45	84	178–179	$C_{19}H_{23}NO_3$	72.82	7.40	4.47	73.00	7.52	4.27	197–198
Ih	CH_3O	CH_3O	H	3	9	64	172–173	$C_{20}H_{25}NO_3$	73.39	8.01	4.28	73.23	7.85	4.15	110–112
Ii	H	CH_3O	CH_3O	2	34	77	137–138	$C_{19}H_{23}NO_3$	72.82	7.40	4.47	72.61	7.31	4.49	225–226
Ij	H	CH_3O		2	13	81	181–182	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	70.19	6.76	4.15	...
Ik	H	CH_3O	H	1	28	71	174–175	$C_{17}H_{19}NO_2$	75.81	7.11	5.20	75.77	7.04	5.19	242–244
Il	H	CH_3O	H	2	44	85	176–177	$C_{18}H_{21}NO_2$	76.40	7.43	4.95	76.33	7.20	4.95	236–238

[a] A = heated without acid catalyst for 5–7 days; B = overnight reflux in presence of trifluoroacetic acid. [b] From ethyl acetate. [c] From acetonitrile–ether (1:1).

TABLE II

SPECTRAL PROPERTIES OF BENZO[a]CYCLOALKANO[f]QUINOLIZINONES (I)

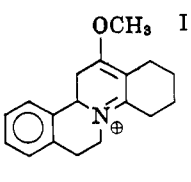
Compd.	λ, mμ (log ε) Cyclohexane	Ethanol	Perchlorate–ethanol	Benzyl proton (τ)[a]
Ia	310 (4.08)	333 (4.17)	333 (4.16)	5.25
Ib	312 (4.05)	336 (4.11)	337 (4.08)	5.29
Ic	318 (4.00)	341 (4.13)	338 (4.14)	5.30
Id	313 (4.07)	335 (4.11)	335 (4.10)	5.30
Ie	310 (4.09)	333 (4.17)	332 (4.17)	5.28
If	312 (4.08)	332 (4.17)	339 (4.10)	5.32
Ig	313 (4.04)	334 (4.11)	335 (4.12)	5.32
Ih	318 (4.06)	340 (4.13)	338 (4.17)	5.31
Ii	312 (4.08)	335 (4.14)	335 (4.15)	5.28
Ij	311 (4.06)	335 (4.09)	...	5.30
Ik	310 (4.08)	333 (4.18)	333 (4.16)	5.28
Il	313 (4.06)	336 (4.12)	336 (4.11)	5.32

[a] In deuteriochloroform. This signal appeared as a 1:1:1:1 quartet with J = 14–15 c.p.s. for the inner signals and J = 4–5 c.p.s. for the outer signals.

I on carbon or nitrogen would give distinctly different chromophores.[13] The large bathochromic shift observed for I in going from cyclohexane to ethanol (Table II) is also worthy of note. In reporting the maxima for cisoid enamino ketones, it is important to specify the solvent used, since such a pronounced solvent effect is encountered.[14] The extinction coefficients of I are lower than transoid enamino ketones[13b] and this is in agreement with other *cis* and *trans* conjugated systems,[15] whereas the maxima[16] for the cisoid systems appear at longer wave lengths than the transoid systems.

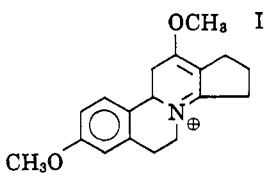
The isoquinoline esters, III, were obtained by two methods: (a) Bischler–Napieralski ring closure of the N-acyl-β-phenethylamines IX (X = $NHCOCH_2$-COOEt) to the dihydroisoquinolines X; and (b) cyclization of the β-phenethyl chlorides IX (X = Cl) with

(13) (a) To exclude the possibility that the spectral similarities of I and I·$HClO_4$ were due to complete ionization of the perchlorate to the free bases, the O-methyl derivatives, **1** and **2**, were examined. The maxima



1

λ^{EtOH} 336 mμ (log ε 4.10)



2

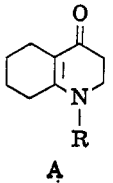
λ^{EtOH} 333 mμ (log ε 4.12)

and ε values agree very well with the corresponding perchlorates (A. I. Meyers and A. H. Reine, unpublished data). (b) After the completion of this work, a report appeared [G. Alt and A. J. Speziale, *J. Org. Chem.*, **30**, 1407 (1965)] which described the ultraviolet method of determining the site of protonation on enamino ketones. The similarity of the spectra of enamino ketones and their perchlorates was also noted.

(14) A similar solvent shift has been observed in the transoid enamino ketones of the type reported in ref. 13b: G. H. Alt and A. J. Speziale, private communication.

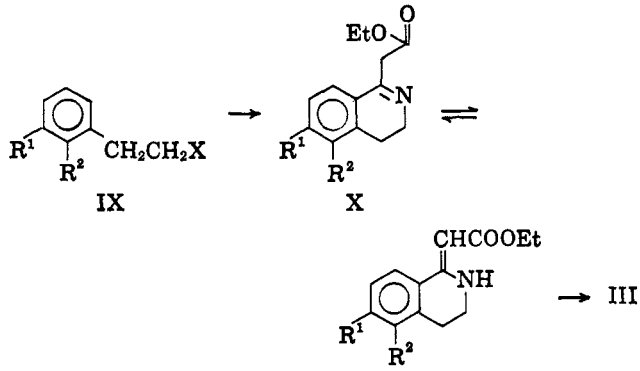
(15) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 16.

(16) Professor M. E. Keuhne, University of Vermont, has informed us that the enamino ketone A, which possesses a cisoid chromophore, absorbs



A

at 335 mμ in ethanol.



a, $R^1 = R^2 = H$
b, $R^1 = OCH_3$; $R^2 = H$
c, $R^1 = H$; $R^2 = OCH_3$
d, $R^1 = R^2 = OCH_3$

ethyl cyanoacetate in the presence of stannic chloride.[17] The dihydroisoquinolines were rapidly reduced to III in ethanol–acetic acid using palladium catalysts. The infrared spectra of Xa–d possessed two carbonyl bands (5.8 and 5.9 μ) suggesting a tautomeric mixture of the *endo* and *exo* forms. The n.m.r. spectrum (CCl_4) confirmed this by exhibiting a vinyl singlet at τ 4.91 equal in area to the NH proton at τ 0.99, and both these signals corresponded to 0.90 of a total proton area. Thus, the *exo* form predominates in the mixture in a ratio of 9:1. The hydrochlorides of X were all single species corresponding to the *endo* structure (*via* C-protonation of the *exo* form).

Experimental Section

All melting points are corrected and were determined on a Fisher-Johns apparatus. N.m.r. spectra were taken on a Varian A-60 instrument.[18] Infrared spectra were determined on a Beckman IR-5A, and ultraviolet spectra on a Beckman DB spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-(Carboethoxymethyl)-3,4-dihydro-5-methoxyisoquinoline (Xc).—A cold solution of 21 g. (0.181 mole) of ethyl cyanoacetate, 21 ml. (0.18 mole) of stannic chloride, and 31.8 g. (0.18 mole) of 2-(*o*-methoxyphenyl)ethyl chloride[19] in 95 ml. of dry nitrobenzene was added dropwise to 380 ml. of stirred nitrobenzene at 120–130° during 45 min. The resulting dark solution was heated for an additional 2 hr. at the same temperature, cooled, and poured into 600 ml. of 20% sodium hydroxide solution at 0–10°. The aqueous mixture was extracted several times with ether and then discarded. The ether extract, after washing with water, was cooled to 0° and washed with 20% hydrochloric acid to remove the isoquinoline. After neutralization with 20% sodium hydroxide at −10 to 0°, the aqueous solution was extracted with ether, the extracts were dried over sodium sulfate, and the ether was removed *in vacuo*. The residual viscous brown oil (14 g.) was dissolved in 100 ml. of 95% ethanol, heated with a solution of 13 g. (0.06 mole) of picric acid in 100 ml. of ethanol, and allowed to stand overnight at 0°. The resulting picrate (16 g.) was recrystallized from ethanol to afford 15.2 g. of pure picrate, m.p. 113–114°. The latter was added portionwise at 0° to a stirred mixture of 200 ml. of 20% sodium hydroxide and 300 ml. of ether. The ether layer was separated, the aqueous solution was extracted several times with ether, and all the ethereal solutions were combined and dried over sodium sulfate. Evaporation of the solvent gave 6 g. (13%) of the isoquinoline: m.p. 65–68°; λ^{CHCl_3} 3.00, 3.33, 3.40, 6.10, 6.22, 6.40 μ.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.88; N, 5.67. Found: C, 68.22; H, 6.89; N, 5.76.

1-(Carboethoxymethyl)-1,2,3,4-tetrahydro-5-methoxyisoquinoline (IIIc).—A mixture of 19.5 g. (0.08 mole) of Xc, 3 g. of 5% palladium on charcoal, 100 ml. of 95% ethanol, and 100 ml. of glacial acetic acid was hydrogenated in a Parr apparatus at 60 p.s.i. The theoretical quantity of hydrogen was absorbed in 45 min. after which the catalyst was removed by filtration and the ethanol was evaporated under vacuum. The residual acetic acid solution was diluted with 50 ml. of water and neutralized by adding potassium carbonate. The alkaline solution was extracted several times with ether, and after drying the extracts over potassium carbonate, the solvent was removed to give 16.6 g. of a viscous oil that would not crystallize: $n^{20}D$ 1.5415; λ^{film} 2.97, 3.40, 3.52, 5.80, 6.32 μ.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.21; H, 7.47; N, 5.79.

The picrate (from ethanol) had m.p. 145–147°.

Ethyl N-(2,3-Dimethoxyphenethyl)malonamate (IXd, X = $NHCOCH_2COOEt$).—A solution of 59 g. (0.32 mole) of 2-(2,3-dimethoxyphenyl)ethylamine[20] (IXd, X = NH_2) and 150 g. (0.93 mole) of diethyl malonate was heated at 110–120° for 19 hr. under a slow stream of nitrogen. The ethanol formed during the reaction was collected in a Dry Ice trap. The excess diethyl malonate was removed under diminished pressure leaving a crystalline residue. Recrystallization from ether gave 89 g. (94%) of the amide: m.p. 60–61°; λ^{CHCl_3} 2.92, 3.35, 3.40, 3.45, 5.80, 5.98, 6.20 μ.

Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.23; H, 7.30; N, 4.92.

1-(Carboethoxymethyl)-3,4-dihydro-5,6-dimethoxyisoquinoline (Xd).—A solution of 48 g. (0.16 mole) of ethyl N-2,3-dimethoxyphenethylmalonamate in 1.1 l. of toluene was heated to boiling and 200 ml. of the solvent–water azeotrope was removed. Three 90-g. portions of phosphorus pentoxide were added in 10-min. intervals and the mixture was refluxed with stirring for 30 min. The heterogenous mixture was cooled to −10° and decomposed with 1.5 l. of ice–water below 0°. The aqueous layer was separated and the toluene layer was extracted several times with 100-ml. portions of 2 *N* hydrochloric acid. After extracting the aqueous layer with ether, the latter was discarded and the acid solution was neutralized with saturated potassium carbonate solution. The oil which had separated was taken up in ether and the solution was dried over sodium sulfate. Evaporation of the ether gave 45 g. (98%) of a crude product, m.p. 72–77°. Recrystallization from petroleum ether (b.p. 30–60°)—acetone (6:1) furnished 30 g. of the base: m.p. 83–84°; λ^{CHCl_3} 2.98, 3.33, 6.08, 6.25, 6.35, 6.75 μ.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.91; H, 7.16; N, 4.98.

The picrate (from ethanol) melted at 165.5–166.0°.

Anal. Calcd. for $C_{22}H_{22}N_4O_{11}$: C, 49.80; H, 4.40; N, 11.05. Found: C, 49.68; H, 4.58; N, 11.15.

1-(Carboethoxymethyl)-1,2,3,4-tetrahydro-5,6-dimethyoxyisoquinoline (IIId).—Hydrogenation at 4 atm. in acetic acid, using 70 mg. of Adams catalyst for 9.5 g. of Xd, gave 9.5 g. (99%) of the tetrahydroisoquinoline: m.p. 71–72°; λ^{CHCl_3} 2.90, 3.31, 5.78, 6.18 μ.

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.65; H, 7.63; N, 5.03.

The picrate (from ethanol) melted at 138–140°.

Anal. Calcd. for $C_{21}H_{24}N_4O_{11}$: C, 49.80; H, 4.84; N, 11.08. Found: C, 49.95; H, 4.75; N, 11.20.

1-(Carbethoxymethyl)-3,4-dihydroisoquinoline (Xa).—A solution of 113 g. (1.0 mole) of ethyl cyanoacetate, 160 g. (1.14 mole) of β-phenethyl chloride, and 260.5 g. (1.0 mole) of anhydrous stannic chloride was heated for 2 hr. at 110–115° and then poured, while still hot, into 1 l. of 20% sodium hydroxide solution. The aqueous solution was kept below 5° by external cooling and addition of ice. The alkaline solution was extracted with ether several times and the extracts were washed with 10% hydrochloric acid. The acid solution was neutralized cautiously with 35% sodium hydroxide and the oil which appeared was taken up in ether. After drying and concentrating the ethereal solution, there remained 108 g. of crude isoquinoline. Distillation of the latter afforded 43 g. (38%) of a pale yellow oil: b.p. 145–146° (0.45 mm.); $n^{25}D$ 1.6154; λ^{film} 2.99, 5.80, 6.09, 6.35 μ.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.88; H, 6.91; N, 6.45. Found: C, 71.94; H, 6.89; N, 6.71.

The picrate (from ethanol) melted at 144–145°.

(17) M. Lora-Tomayo, R. Madrenero, G. G. Munoz, J. Marzal, and M. Stud, *Ber.*, **94**, 199 (1961), and earlier reference cited therein.

(18) Purchased with funds granted by the National Science Foundation (Gp-3674).

(19) E. Hardegger, D. Redlich, and A. Gul, *Helv. Chim. Acta*, **28**, 628 (1945).

(20) A. Lindenmann, *ibid.*, **32**, 69 (1949).

1-(Carbethoxymethyl)-1,2,3,4-tetrahydroisoquinoline (IIIa).—A solution of 50 g. (0.23 mole) of Xa in a 150 ml. of 1:1 acetic acid–ethanol, containing 5 g. of 5% palladium on carbon, was hydrogenated at 4 atm. The hydrogen absorption was complete after 1 hr. The ethanol was evaporated and the acetic acid solution was neutralized with potassium carbonate. The oil which appeared was taken up in ether and dried over sodium sulfate. Concentration of the ether solution gave 50.2 g. of crude product. Distillation of the latter afforded 47.1 g. (93%) of the reduced product: b.p. 120° (0.4 mm.); $n^{25}D$ 1.5337; λ^{film} 2.96, 5.80 μ.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.20; H, 7.93; N, 6.40.

1-(Carboethoxyethyl)-3,4-dihydro-6-methoxyisoquinoline (Xb) and 1-(carboethoxyethyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (IIIb) were prepared by the method described by Nelson, *et al.*[21]

Formation of Ia and V (Ethylene Glycol Procedure).—A solution of 10.0 g. (0.05 mole) of IIIa, 8.4 g. (0.1 mole) of cyclopentanone, and 100 ml. of toluene was refluxed with azeotropic removal of water for 72 hr. Examination of an aliquot after 48 hr. indicated no further increase in the enamine band at 1642 cm.$^{-1}$. The toluene was removed under reduced pressure and 150 ml. of freshly distilled ethylene glycol was added to the residue. The dark solution was heated for 15 hr. at 170–180° and after cooling to room temperature was diluted with 400 ml. of chloroform. The homogeneous solution was washed five times with 200-ml. portions of water and the organic layer was dried over sodium sulfate. Removal of the chloroform left a waxlike mass (11.4 g.) which deposited a crystalline solid upon the addition of petroleum ether. The solid (3.1 g.) was collected by filtration and only partially dissolved in hot ethyl acetate. Filtration of the latter solution gave 0.45 g. of a high-melting solid, whereas the filtrate, upon cooling, deposited 1.9 g. (20%) of Ia. The ethyl acetate insoluble product, V, had m.p. 259–260° (from ethanol); λ_{max}^{EtOH} 286 mμ (log ϵ 4.23), 256 (4.57); and a vinyl singlet ($CDCl_3$) at τ 3.19.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.99; H, 6.58; N, 5.87.

Formation of Id and V (Ethylene Glycol Method).—The isoquinoline ester IIIa and 4-methoxycyclohexanone were treated as above to yield 24% of Id and 7% of VI: m.p. 203–205°; λ_{max}^{EtOH} 282 mμ (log ϵ 4.17), 256 (4.50); λ^{CHCl_3} 6.1 μ; vinyl singlet ($CDCl_3$) at τ 3.21.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.66; H, 6.91; N, 5.02.

Benzo[*a*]cycloalkano[*f*]quinolizinones (I). A.—A solution of 0.1 mole of the appropriate isoquinoline ester, 0.20 mole of the ketone (IV), and 100 ml. of toluene was heated in the presence of a Dean–Stark trap for 5–7 days. Although water was observed in the trap during the initial period of the reaction, the solution gradually became homogeneous. At the end of the heating period the solvent was evaporated under aspirator pressure and subsequently under oil pump pressure. The viscous oil that remained was triturated with petroleum ether causing a crystalline solid to precipitate. The latter was collected by filtration and recrystallized from a minimum amount of ethyl acetate.

B.—The same ratio of reactants and solvents was employed and, in addition, 1–3 ml. of trifluoroacetic acid was added. The solution was refluxed with azeotropic water removal for 15–30 hr., cooled to room temperature, and washed first with bicarbonate and then with water. After drying over sodium sulfate, the toluene was evaporated as in part A. The residual oil in most cases solidified, but in those cases where it did not, the addition of petroleum ether caused immediate precipitation of the product. The latter was then purified by recrystallization from ethyl acetate.

Perchlorate salts were prepared by adding 1:1 perchloric acid–ether to an alcoholic solution of I. The salt crystallized on standing or with subsequent cooling. Purification was achieved by recrystallization from 1:1 acetonitrile–ether.

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The Methylation of Enamines of 1-Azabicycloalkanes[1]

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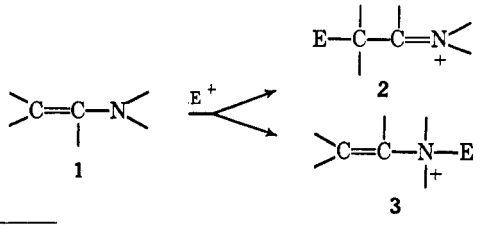
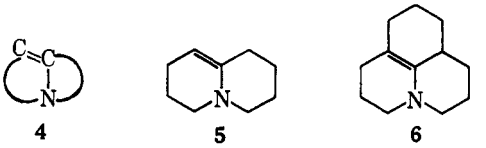
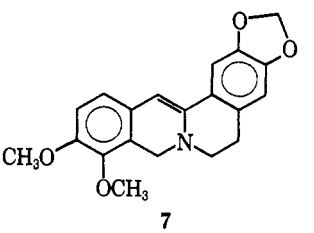
The methylations of several indolizidine and quinolizidine enamines with methyl iodide were studied. The major products were the N-monomethyl derivatives except in the case of the indolizidine enamine **9**, which underwent exclusive C-monomethylation as well as extensive dimethylation. The unique behavior of **9** is rationalized in terms of I strain in the transition state leading to N- but not to C-methylation.

Enamines (**1**) are ambident nucleophiles which may react with electrophilic reagents either at carbon or nitrogen to give **2** or **3**, respectively.[3] With simple alkyl halides the enamines of aldehydes appear to give only the vinyl quaternary ammonium salts[4] (**3**), while the enamines of cyclic ketones form both C- and N-alkylated products in varying proportions depending on, among other things, the structures of the starting enamines.[5] Much less is known about the position of alkylation of enamines of 1-azabicycloalkanes of the general structure **4**; $\Delta^{1(10)}$-dehydroquinolizidine[6] (**5**)







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(5) (a) G. Opitz, H. Mildenberger, and H. Suhr, *ibid.*, **649**, 47 (1961); (b) G. Stork, XVIth National Organic Symposium Abstracts, Seattle, Wash., June 1959, p. 44.