isomeric **13** is a further reflection of the relative stabilizing effects of nitro and cyano groups on Meisenheimer complexes (*vide supra*). In **10**, the entering methoxyl group is situated *para* to the nitro substituent, while in the presumably less stable **13** an *ortho* relationship is present. This selectivity in substitution is paralleled by the relative stabilities of complexes **3** and **4**. In the former complex, the entering methoxyl group is *para* to a nitro function and the complex is more stable by an order of magnitude than **4**, a complex for which only *ortho* relationships between the entering methoxyl and nitrogroups are present. Similarly, in the reaction of methoxide ion with 2,4-dicyano-6-nitroanisole, attack of methoxide ion is specific at the position *para* to the nitro substituent to yield **14**; no evidence was obtained for attack of methoxide at the position *ortho* to the nitro group.[1] It is thus apparent that the same factors which determine the relative stabilities of the cyanodinitro complexes **3** and **4** and the dicyanonitro complex **7** also determine the position of attack in the formation of the 1,3 complexes **10** and **14**.

Registry No.—**1**, 19019-04-6; **2**, 19018-96-3; **3**, 12247-59-5; **4**, 12321-51-6; **5**, 1270-28-6; **6**, 606-35-9; **10**, 12321-50-5; **12**, 12321-49-2; sodium methoxide, 124-41-4;.

Acknowledgment.—This study was supported in part by a grant from the U. S. Atomic Energy Commission. A portion of the pmr studies were carried out with instrumentation provided by a grant (FR 00292-03) from the National Institutes of Health. We are indebted to Drs. W. E. Byrne and B. D. Martin for assistance in the determination of pmr spectra.

The Chemistry of Cyclic Enamino Ketones. IV. Factors Affecting C and O Alkylation[1]

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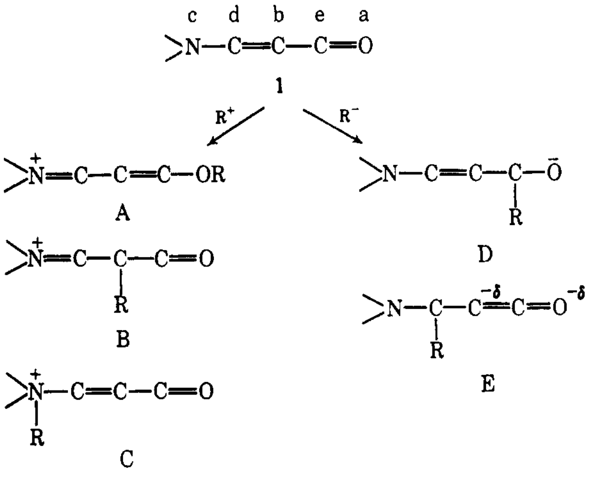
Received August 26, 1968

The reaction of *cis*- and *trans*-enamino ketones with alkyl halides has been investigated with emphasis upon solvent and steric effects. For *cis*-enamino ketones, aprotic solvents produced mixtures of the C- and O-alkyl salts, whereas protic solvents yielded mixtures of the O-alkyl and O-protonated salts. Possible mechanisms leading to the latter products are discussed. Alkylation on nitrogen was never observed in any of the cases examined. The results of this study clearly demonstrate the ability of the solvent to decide the course of an enamino ketone alkylation reaction. With data from enamino ketones having six-, seven-, and eight-membered fused rings now available, the effect of ring size on the site of alkylation is summarized as well as the influence of the alkyl halides. The reactions of *trans*-enamino ketones with alkyl iodide are essentially insensitive to solvent and gave exclusively O-alkyl derivatives.

The enamino ketone (β-amino-α,β-unsaturated carbonyl) moiety, **1**, represents an area of considerable synthetic scope when one considers that there are present in this group three nucleophilic sites (a, b, and c) and two electrophilic sites (d and e) available for reaction. Thus, electrophilic addition could lead to adducts A, B, and C while nucleophilic addition could provide D and E (Scheme I). If the factors affecting the sites of addition can be understood and brought under control, there would be available a synthetic pathway to a variety of substances inaccessible by other means. We have previously demonstrated, in brief reports,[3,4] that the enamino ketone group is indeed versatile and capable of reacting with electrophilic and nucleophilic agents under varying sets of conditions. The problem of the site of alkylation on systems such as **1** (leading to A, B, and C) appeared to be sufficiently complex, however, that further studies were obviously necessary. A search of the literature revealed that Leonard and Adamcik[5] had made the only systematic attempt to determine sites of alkylation in acyclic enamino ketones, **2**, and monocyclic *trans*-enamino ketones, **3**. The reaction conditions were limited to prolonged heating of the substrate with an excess of alkyl halide.

SCHEME I



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[1] This study supported by the National Institutes of Health (RG-06248-08).

[2] Taken from the Ph.D. Dissertation of A. H. Reine, June 1968. Financial support (to A. H. Reine) by the Eli Lilly Co., Indianapolis, Ind., is gratefully acknowledged.

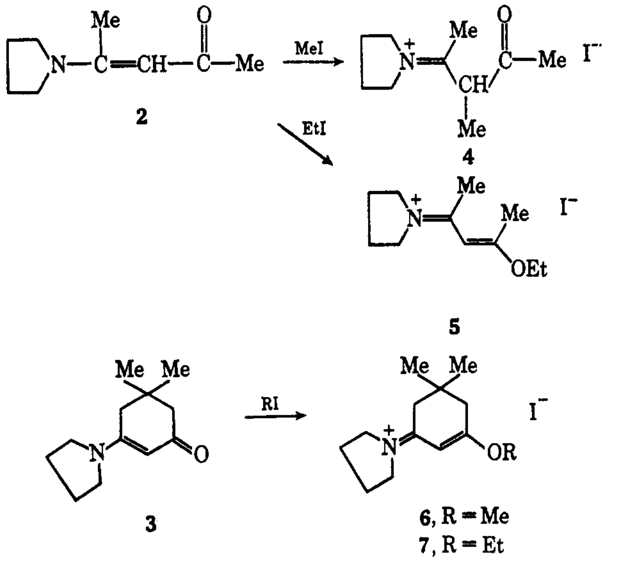
[3] A. I. Meyers, A. H. Reine, and R. Gault, *Tetrahedron Lett.*, No. 41, 4049 (1967).

[4] A. I. Meyers and S. Singh, *ibid.*, No. 52, 5319 (1967).

[5] N. J. Leonard and J. A. Adamcik, *J. Amer. Chem. Soc.*, **81**, 595 (1959), and previous references cited therein.

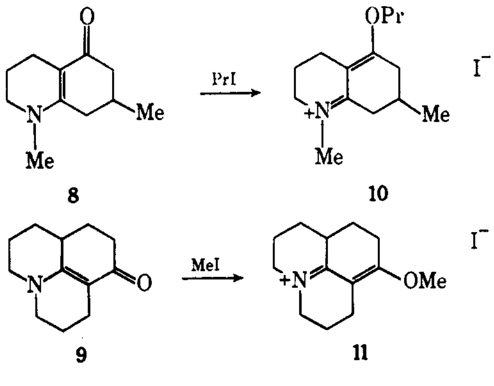
The reaction of **2** with methyl iodide produced the C-methiodide, **4**, as the major product, whereas ethyl iodide furnished only the O-ethiodide, **5** (Scheme II). In contrast to these results, the monocyclic *trans* system (**3**), on reaction with alkyl iodides, led solely to O-alkylated derivatives, **6** and **7**.

SCHEME II

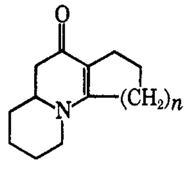


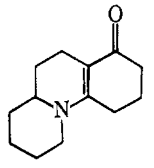
The cyclic enamino ketones, **8** and **9**, have been reported[6,7] to yield only the corresponding O-alkylated derivatives, **10** and **11**, when treated with alkyl halides (Scheme III). Thus, the only example of C alkylation was reported in the acyclic system, **2**. The fact that becomes immediately clear from these limited data is that the enamino ketones possessing a fixed *trans* configuration (**3**, **8**, and **9**) exhibit O alkylation as the sole path of the reaction. The alkylation observed in **2** could conceivably have arisen from the *cis* form which is known to be in equilibrium with the *trans* isomer.[8]

SCHEME III



Experiments were therefore carried out to assess the influence of solvent, alkyl halide, ring size, and *cis* and *trans* configuration upon the site of alkylation. The readily available tricyclic derivatives, **12** and **13**, were chosen as suitable candidates for these studies since they possessed rigid *cis*-[9] and *trans*-enamino ketone[10] moieties.


12, $n = 1-4$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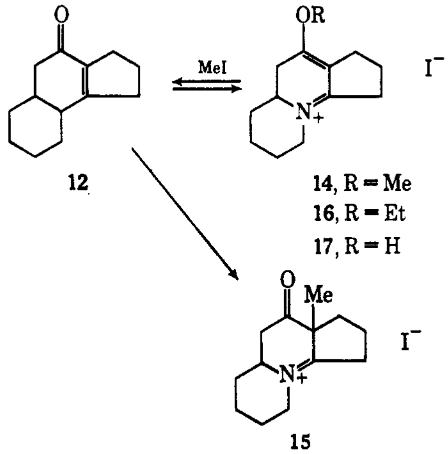
Discussion

***cis*-Enamino Ketones.**—Alkylation studies were performed in detail using **12** ($n = 1$) and methyl iodide in a variety of solvents (Table I). It can be seen that, under the conditions examined, it is possible to obtain the O-methyl (**14**), the C-methyl (**15**), the O-ethyl (**16**), and the O-protonated (**17**) derivatives (Scheme IV). All of these products have been isolated from the reaction mixtures and were completely characterized (*cf.* Experimental Section).

SCHEME IV



Methylation in aprotic solvents produced varying amounts of mixtures containing only the O-methyl (**14**) and the C-methyl (**15**) salts, with the latter predominating in all cases. The extent of alkylation appeared to follow the decreasing order of dielectric constants (and Z values) of the solvents employed. Thus, aprotic solvents of high ionizing power produced the highest yield of alkylated products (60–64%) during 48 hr of heating, whereas solvents of poor ionizing ability resulted in low yields (10–20%) of products. Since all methylation reactions were performed under identical conditions, these data may be regarded as approximate relative rates and it may be concluded from this that there is considerable charge development in the transition state leading to **14** and **15**. The effect of protic solvents on the extent of reaction appears to be slight although the dielectric constants of these solvents vary appreciably. It can be stated that, in alcoholic solvents which are capable of hydrogen bonding to the

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(6) H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, No. 18, 1279 (1965); G. V. Kondrateva, V. I. Gunar, L. F. Overchkina, S. I. Zavyalov, A. I. Krotov, and N. D. Zelinski, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **3**, (1967).

(7) Z. Valenta, P. Deslongchamps, R. A. Ellison, and K. Wiesner, *J. Amer. Chem. Soc.*, **86**, 2533 (1964).

(8) G. O. Dudek and G. P. Volpp, *ibid.*, **85**, 2697 (1963); H. E. A. Kramer, *Ann.*, **696**, 15 (1966).

(9) A. I. Meyers, A. H. Reine, J. C. Sircar, K. B. Rao, S. Singh, H. Weidmann, and M. Fitzpatrick, *J. Heterocycl. Chem.*, **5**, 151 (1968).

(10) N. A. Nelson and Y. Tamura, *Can. J. Chem.*, **43**, 1323 (1965).

TABLE I

REACTION OF **12** ($n = 1$) WITH METHYL IODIDE IN VARIOUS SOLVENTS[a]

Solvent	Dielectric constant	*Z* values[b]	Over-all[c] yield, %	O-Me (**14**), %	C-Me (**15**), %	OH (**17**), %
Aprotic						
Acetonitrile	37.5	71.3	64	48[d]	52[d]	
Benzonitrile	25.2		63	21	79	
Dimethylformamide	37.8	68.5	60	10	90	
Nitrobenzene	34.8		60	20	80	
Ethyl acetate	6.0		15	7	93	
Benzene	2.3	54.0	10	3	97	
Tetrahydrofuran	7.0		18	2	98	
Methyl iodide	7.0		20	10	90	
Protic						
Methanol	33.0	83.6	72	60[e]		40
Ethanol	24.0	79.6	75	35[f]		65
2-Propanol	18.0	76.3	76			100
2-Methyl-2-propanol	10.9	71.3	56			100
Trifluoroethanol	27~	←———	———	No reaction	———	———→

[a] All reactions performed at 50 ± 2° for 48 hr. [b] See ref 11. [c] Remainder of material was isolated as unreacted **12**; material balance was 90–98%. [d] The composition of the mixtures of C- and O-methyl salts was determined by the ultraviolet (uv) spectrum of **14** [λ_{max} 334 mμ (ϵ 12,600)] and nmr spectrum of **14** (O-methyl singlet at τ 5.87). The method was accurate to ±2%. [e] The composition of the mixture (**14** and **17**) was determined by Beer–Lambert plot of A_{334} *vs.* concentration of **17** [λ_{max} 334 mμ (ϵ 16,600)] in authentic mixtures of **17** and **14** [λ_{max} 334 mμ (ϵ 12,600)] and of **17** and **16** [λ_{max} 334 mμ (ϵ 11,600)]. The method was based upon differences in extinction coefficients (ϵ) for **14**, **16**, and **17** and was accurate to ±5%. [f] Product obtained was the O-ethyl salt, **16**.

oxygen atom in **12**, charge development is not very important in approaching the transition state. A similar effect has also been noted in the reaction of pyridine with ethyl iodide in alcoholic solvents.[11]

Aprotic Solvents.—The striking fact seen from methylation in the aprotic solvent is the considerable preponderance of C-methyl product obtained. The comparable rate of C- to O-methyl salt in acetonitrile appeared to be anomalous and this system was examined more closely. It was found that, when a solution of **14** in acetronitrile was heated at 50° for 6 hr, there was obtained, after removal of the solvent, a mixture containing recovered **14** (30%) and the enamino ketone **12** (70%). This reversal of the O-methyl salt to **12** can only be understood in terms of nucleophilic displacement on the methyl group by the iodide ion. To further substantiate this idea, the O-methyl salt was heated (50°) for 2 hr in acetronitrile in the presence of 5 equiv of sodium iodide. As expected, the iodide ion present in higher concentration completely converted the O-methyl salt into **12.** Finally, when **14** was converted into its perchlorate salts, **14a** (utilizing silver perchlorate), and heated for 12 hr in acetonitrile, no reversal to the enamino ketone took place. The perchlorate ion is undoubtedly too poor a nucleophile to perform this task. With the reversible nature of the O-methylation process firmly established, it was necessary to examine the C-methyl salt (**15**) for the unlikely possibility that it, too, would undergo demethylation. This behavior was checked by merely recovering **15** unchanged after prolonged heating in acetonitrile. The data in Table I which indicate that all aprotic solvents, except acetonitrile, provide a medium for substantial C methylation appeared, therefore, to be fortuitous. A study was undertaken to determine the ratio of C- to O-methyl salts when methylation was carried out at different time periods in acetronitrile. The interesting results obtained are shown in Table II.

TABLE II

REACTION OF **12** ($n = 1$) WITH METHYL IODIDE IN ACETONITRILE (50 ± 2°)

Hours	**14**, %[a]	**15**, %	Over-all yield, %[b]
3	92	8	27
6	85	15	40
12	72	28	52
48	48	52	64
96	36	63	74

[a] Product composition determined as in Table I. [b] Total of **14** + **15**; remainder of material was isolated as unreacted **12**.

It is evident that O methylation is kinetically favored and predominates in the early stages of the reaction. Thus, the data in Table I which contains all alkylations at 48 hr simply reveals the C- to O-methyl ratio after that time period. As longer reaction times are allowed, the amount of C-methyl product increases owing to the irreversible nature of this process. It is noteworthy that the amount of O-methyl salt obtained in acetonitrile was considerably greater than that obtained from dimethylformamide (DMF) although the dielectric constants and the *Z* values for these two solvents are rather close.[12] The predominance of the C-methyl product from reaction in DMF is undoubtedly due to a faster rate of reversal (**14** → **12**) in this solvent. This interpretation was substantiated when **14,** on treatment in DMF under usual reaction conditions for 6 hr, yielded only the enamino ketone **12.** Similar treatment in acetonitrile, as previously mentioned, yielded a mixture of **12** and **14.** Rates of bimolecular substitution reactions with nucleophilic anions are known to be highly accelerated when carried out in dipolar aprotic

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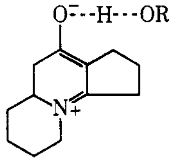
[11] E. M. Kosower, *J. Amer. Chem. Soc.,* **80,** 3267 (1958). For detailed discussions on this and related topics, see E. M. Kosower, "An Introduction to Physical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1968, p 317.

[12] Since it is known that alkyl halides react with DMF [N. Kornblum and R. K. Blackwood, *J. Amer. Chem. Soc.,* **78,** 4037 (1956)], the possibility that methyl iodide forms an adduct with DMF which then reacts with enamino ketone **12** can not be discounted. However, from results with other alkylating agents, such a bulky adduct would be expected to give a predominance of the O-methyl salt, **14,** over the C-methyl derivative, **15.**

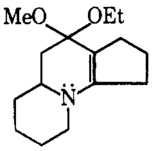
solvents such as dimethylformamide and dimethyl sulfoxide.[13,14]

Protic Solvents—The reaction of **12** with methyl iodide followed a rather different course in protic solvents (Table I). The use of methanol afforded a mixture of the O-methyl salt, **14**, and the hydriodide salt, **17**. When the reaction was conducted in ethanol, a mixture of O-ethyl (**16**) and hydriodide (**17**) salts was obtained. In contrast to these results, the enamino ketone **12** was quantitatively recovered upon attempted methylation in 2,2,2-trifluoroethanol. Furthermore, the total absence of C-methyl salts in the above as well as in propanol-2 and 2-methyl-2-propanol and the fact that only the hydriodide salt, **17**, was obtained in the latter two solvents is also unexpected.

The absence of any reaction occurring in trifluoroethanol is attributed to the strong hydrogen-bonding capacity of this solvent[15] resulting in the destruction of the nucleophilic character of the oxygen atom in **12**. However, hydrogen bonding by weak protic solvents effectively increases the nucleophilic nature of the oxygen by stabilizing the dipolar form, **18**, which accounts for the O alkylation. The O-ethyl salt, **16**, was found to arise when the reactions were performed in ethanol. Solvent attack resulting in alkoxyl exchange must have occurred *via* an addition–elimination process which involved the intermediate **19**. This was confirmed by dissolving the pure O-methyl salt in ethanol and under the typical alkylation conditions (50°) the O-ethyl derivative was produced in quantitative yield. This facile substitution of the methoxyl group was also observed by treating either the O-methyl (**14**) or the O-ethyl (**16**) derivatives with anhydrous ammonia in acetonitrile. The aminodihydroquinolizium salt, **20**, was formed quantitatively in a few minutes at room temperature.



18



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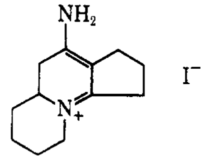
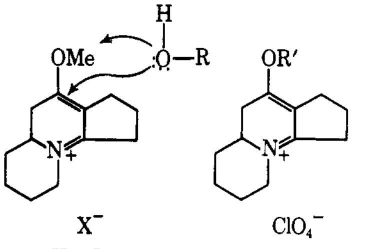


20

The effect of the steric bulk of the solvent molecules in the methylation of **12** was also investigated. Examination of Table I reveals that the only product obtained in propanol-2 or 2-methyl-2-propanol was the hydriodide salt, **17**. Some insight into this process was gained when the O-methyl salt, **14**, was treated with 2-methyl-2-propanol under the alkylation conditions. Although **14** produced only the enamino ketone **12**, replacing the iodide ion by perchlorate (**14a**) and again heating in 2-methyl-2-propanol produced *t*-butylmethyl ether (**21**) and the perchlorate salt (**22**). Thus, the bulky solvent molecule has demonstrated that, if it cannot attack at the ring carbon, it will displace the enamino ketone, which should be a reasonably good leaving group. That only the perchlorate salt, **14a**, exhibited this behavior is readily understood since the iodide ion would be expected to be a more powerful nucleophile than 2-methyl-2-propanol. The same reaction was repeated using propanol-2 and, when the O-methyl iodide salt (**14**) was employed, only reversal to **12** was observed. However, when the O-methyl perchlorate, **14a**, was similarly treated, there was obtained perchlorate salt, **22**, the O-*iso*propyl salt, **23**, and isopropylmethyl ether, **24**. In this system the iodide ion, once again, overshadows any attempts by the solvent to compete as a nucleophile. However, the use of the perchlorate salt allows both alkylation processes to occur, namely attack at the ring carbon as well as at the O-methyl group. A trend is therefore seen in passing from methanol to ethanol to propanol-2 to 2-methyl-2-propanol. The bulkiest solvent is restricted to substitution at the OCH_3 group and the smaller solvent molecules attack preferentially at the most electrophilic ring carbon (as well as at the OCH_3 group). Propanol-2, borderline in size, reacts slowly at the ring carbon thus allowing time for reaction at the OCH_3 group to compete effectively. Armed with this information on the behavior of the O-methyl derivative, a reinvestigation of the methylation reaction (Table I) was performed in propanol-2 and 2-methyl-2-propanol in anticipation of finding the ethers, **21** and **24**, as additional products to the hydriodide salts. After treatment of **12** and methyl iodide in propanol-2 as well as 2-methyl-2-propanol, the solvents were carefully evaporated and collected in Dry Ice traps. Gas chromatography revealed the presence of the ethers **21** and **24**, whose structures were confirmed by comparison with authentic samples. It is possible that other mechanisms are also operating to produce these results. It has already been shown that nucleophilic solvent attack *does* occur at the O-methyl group to give the ethers; however, a simultaneous reaction involving a base assisted nucleophilic displacement (Scheme V) cannot be discounted. On the other hand, the possibil-



+ MeOR

21, R = *t*-Bu

24, R = *i*-Pr

14, X = I

14a, X = ClO_4

22, R′ = H

23, R′ = i-Pr

TABLE III

EFFECT OF RING SIZE IN REACTIONS OF *cis*-ENAMINO KETONES WITH METHYL IODIDE[a]

12, *n*	pK_a[b]	Over-all yield,[c] %	OCH_3, %	CCH_3, %
1	2.98	64	48[d]	52
2	2.82	24	75[e]	25
3	2.83	70	53[e]	47
4		50		100[f]

[a] All reactions conducted in acetonitrile at 50 ± 2° for 48 hr. [b] pK_a's were determined by aqueous potentiometric titration of the hydriodide salts of the enamino ketones (n = 1, 2, 3, 4) with standardized sodium hydroxide solution. [c] Total of **24** and **25**; remainder of material was isolated as unreacted enamino ketone. [d] Product composition was determined as in Table I. [e] Products were identified by infrared (ir) and nmr spectroscopy (*cf.* Experimental Section). [f] The isolated methiodide derivative proved to be highly hygroscopic and was therefore quantitatively converted into the corresponding perchlorate salt, mp 118–120°.

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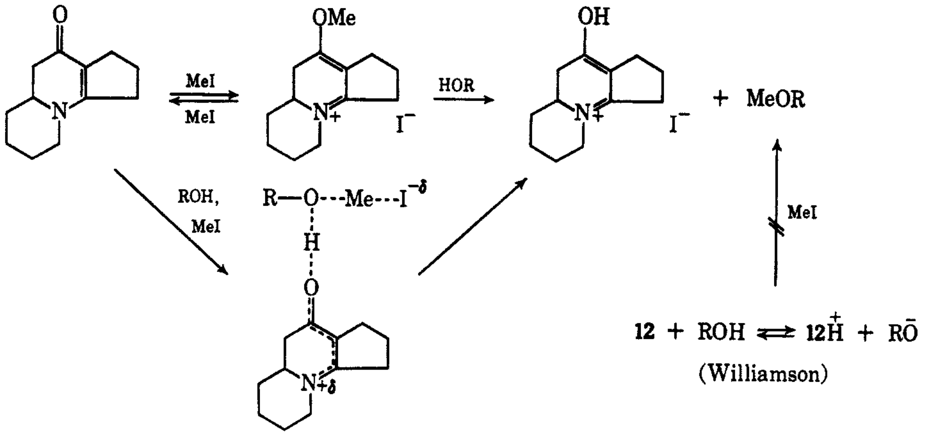
(13) B. A. Feit, J. Sinnreich, and A. Zelkha, *J. Org. Chem.*, **32**, 2570 (1967).

(14) A. J. Parker, *Advan. Org. Chem.*, **5**, 1 (1965).

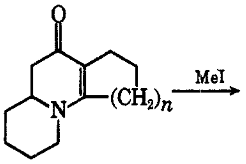
(15) N. Kornblum, P. J. Berrigan, and W. J. LeNobel, *J. Amer. Chem. Soc.*, **85**, 1141 (1963); **82**, 1257 (1960).

SCHEME V

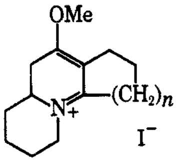


ity of a Williamson-type mechanism has been ruled out on the basis that the enamino ketones **12** are rather weak bases (pK_a 2.8–2.9, Table III, p 701).

Effect of Ring Size.—To explore further the scope and limitations of the alkylation reactions of *cis*-enamino ketones, the derivatives containing six-, seven-, and eight-membered fused rings (**12**, n = 2, 3, and 4) were investigated. The data in Table III shows that after 48 hr the C- and O-alkylated derivatives, **25** and **26**, respectively, were formed in varying amounts depending upon the fused ring size. Since it was found that the O-methyl derivative underwent reversal in acetonitrile, the ratio of **25** to **26** in Table III reflect relative rates and progress of the reactions after 48 hr.

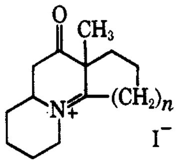


12, n = 2, 3, 4



25

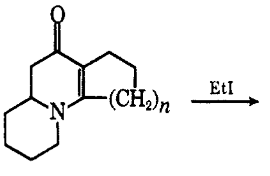
+



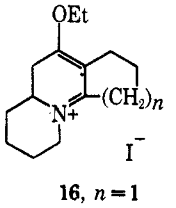
26

The extent of the reactions for five-, seven-, and eight-membered fused rings were comparable, whereas the six-membered fused ring (**12**, n = 2) was alkylated poorly. More significantly, the ratio of **25** to **26** was 3:1 for the six-membered fused ring. The low yield of the latter (24%) can be attributed to rapid reversal to **12** (n = 2) since the starting material is probably more thermodynamically stable than the O-methyl salt (**25**, n = 2). This is based upon known strain theory[16] which states that exocyclic double bonds are more easily accommodated in five- and seven-membered rings than in six-membered rings. This interpretation can be extended to include the eight-membered-ring system, **26** (n = 4), reported to accept readily exocyclic double bonds.[17] It is not immediately apparent why C methylation should be so facile in the eight-membered derivative and why no O-methyl product (**25**, n = 4) was detected. Differences in stabilities of *exo* double bonds, noted in the above systems, would be greatly reflected in the transition states for C methylation. On this basis, a greater amount of C-methyl salt would be expected from systems having five-, seven-, and eight-membered fused rings owing to a lower energy of activation for the formation of **26** compared with those having six-membered rings.

Alkyl Halides.—The effect of alkyl halides on the course of alkylation of *cis*-enamino ketones was briefly investigated in the reactions of ethyl iodide with **12** (n = 1 and 2). In both cases, the corresponding O-ethyl salts, **16** and **27**, were the only products. It should be noted that widely differing results have been obtained in reactions of methyl and ethyl iodide with open-chain enamino ketone systems and that there has never been any report of C ethylation of enamino ketones.[5]

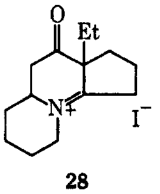


12



16, n = 1
27, n = 2

The reason for the observance of only O ethylation in reactions of **12** (n = 1 and 2) with ethyl iodide may be found in an examination of molecular models which suggest a considerable amount of nonbonded interaction between the angular ethyl group and the β hydrogen (α to the carbonyl function) in the C-ethylated derivative, **28**. This type of steric interaction being absent in the O-ethyl derivatives would tend to favor their formation over **28**.



28

***trans*-Enamino Ketones.**—Investigation of **13** in a

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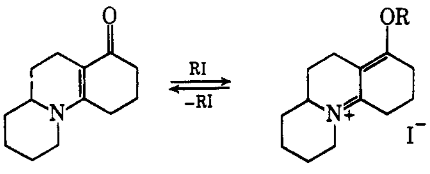
[16] H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954); H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

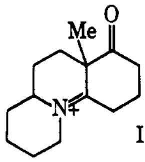
[17] P. von R. Schleyer, *ibid.*, **86**, 1854 (1965).

manner similar to the studies performed on **12** proved that the previous literature[5–7] could be substantiated. In every solvent studied, only O alkylation occurred and no trace to C-alkylated product (**32**) could be detected. The reversibility of the O-methyl (**29**) and the O-ethyl (**30**) salts were, as expected, observed as well as the labile nucleophilic displacement of the alkoxyl group by ammonia producing **31**.



13

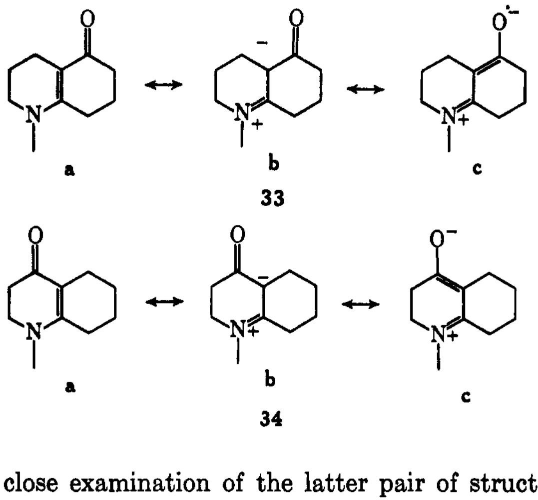
29, R = Me
30, R = Et
31, R = NH$_2$



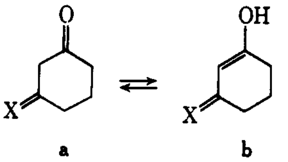
32

In summary, the *trans*-enamino ketones appear to be nucleophilic only at the oxygen atom producing only O-alkylated derivatives. Changes in solvents do not alter the electronic distribution in the ground state (**33a–c**) which seem to be most adequately described by **33a** and **33c**. Structure **33b** is therefore not significant in either the ground state or the transition state leading to alkylation. For the *cis*-enamino ketones, the dipolar structures **34b** and **34c** have been shown to possess comparable significance at least in the transition state. This may be due to a much smaller difference in energy between **34b** and **34c** than that which exists between **33b** and **33c**.

SCHEME VI



A close examination of the latter pair of structures reveals a familar phenonemon, namely the enolization of β diketones, **35** (X = O), which lies almost exclusively in the more stable enolic form (**35b**).[18] A similar situation can be envisioned with the *trans*-enamino ketone **35** (X = N), which may account for the lack of C alkylation.



35

Experimental Section[19]

1,2,3,4,4a,5,7,8-Octahydro-6-methoxy-9H-cyclopentano[*c*]quinolizinium Iodide (14).—A mixture of 1.0 g (5.2 mmol) of **12** and 5 ml of methyl iodide in 15 ml of acetonitrile was heated at 56° for 3 hr. After cooling to room temperature and dilution with ethyl acetate, the mixture deposited 0.400 g (21%) of colorless crystals, mp 115–118°. Analysis of this material by ultraviolet (uv) spectroscopy indicated a mixture of **15** (10%) and **14** (90%). Recrystallization from acetonitrile–ethyl acetate provided a yield of 0.30 g (17%) of **14** as colorless needles: mp 125–127°; ir (CHCl$_3$) 5.95 (m) and 6.40 (s) μ; uv (EtOH) 334 mμ (ϵ 12,600); nmr (CDCl$_3$) τ 5.85 (s, 3 H, OCH$_3$).

Anal. Calcd for C$_{13}$H$_{20}$NOI: C, 46.85; H, 6.05. Found: C, 46.86; H, 5.99.

1,2,3,4,4a,5,7,8-Octahydro-6a-methyl-6H,9H-6-oxocyclopentano[c]quinolizinium Iodide (15).—A mixture of 0.50 g (2.6 mmol) of **12** and 5 ml (10.0 g, 70 mmol) of methyl iodide in 15 ml of tetrahydrofuran on heating at 50° for 48 hr, deposited 87 mg (19%) of colorless crystals: mp 170–190°; ir (CHCl$_3$) 5.78 (s), 5.95 (m), and 6.40 (w) μ; uv (EtOH) 334 mμ. Recrystallization from acetonitrile–ethyl acetate gave pure **15**: mp 201–203°; ir (CHCl$_3$) 5.78 (s) and 5.95 (m) μ; nmr (CDCl$_3$) τ 8.37 (s, 3 H, CCH$_3$).

Anal. Calcd for C$_{13}$H$_{20}$NOI: C, 46.85; H, 6.05. Found: 46.74; H, 5.89.

Hydriodide Salt of 12.—A solution of 1.0 g (5.2 mmol) of enamino ketone **12** in 25 ml of ether was treated with a mixture of 5.0 ml of hydrogen iodide (40%) in ether and ethanol. Dilution with excess ether and cooling afforded 1.52 g (94%) of **17** as off-white needles, mp 165–171°. Recrystallization from acetonitrile–ether gave a pure sample: mp 171–173°; uv (EtOH) 334 mμ (ϵ 16,700); ir (CHCl$_3$) 5.95 (m), 6.45 (s, broad), and 6.80 (s) μ.

Anal. Calcd for C$_{12}$H$_{18}$NOI: C, 45.15; H, 5.68; N, 4.38. Found: C, 45.34; H, 5.77; N, 4.13.

1,2,3,4,4a,5,7,8-Octahydro-6-ethoxy-9H-cyclopentano[*c*]quinolizinium Iodide (16).—A mixture of 1.0 g (5.2 mmol) of **12**, 5 ml of ethyl iodide, and 10 ml of acetonitrile was heated at 55° for 48 hr. Dilution with ether yielded 0.330 g (20%) of crude **16** as a crystalline solid, mp 126–141°. Recrystallization from acetonitrile–ether gave an analytically pure sample: mp 142–145°; ir (CHCl$_3$) 5.95 (m), 6.40 (s), and 6.80 (s) μ; uv (EtOH) 334 mμ (ϵ 11,000); nmr (CDCl$_3$) τ 5.57 (J = 8 Hz, q, 2 H) and 8.55 (J = 8 Hz, t, 3 H).

Anal. Calcd for C$_{14}$H$_{22}$NOI: C, 48.43; H, 6.39; N, 4.03. Found: C, 48.44; H, 6.42; N, 4.16.

Reactions of Enamino Ketone (12, *n* = 1) with Methyl Iodide in Aprotic Solvents. General Method.—All reactions were carried out at 50 ± 2° for 48 hr in nitrogen atmosphere using 0.50 g (2.6 mmol) of **12** (n = 1), 5 ml (10.0 g, 70 mmol) of methyl iodide, and 15 ml of anhydrous solvent. The product composition was qualitatively determined by ir and nmr spectroscopy, utilizing the ir of **15** (5.75 μ) and of **14** (6.40 μ) and the O-methyl singlet of **14** (τ 5.85) and the C-methyl singlet of **15** (τ 8.37). Quantitative estimation of the product composition was made by uv spectroscopy utilizing the λ_{max} of **14** [334 mμ (ϵ 12,600)]. The method was accurate to ±2%.

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[18] E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 811 (1953); R. B. Woodward and E. R. Blout, *J. Amer. Chem. Soc.*, **65**, 562 (1943).

[19] The instrumentation utilized included Varian A-60 for nmr spectra, Beckman IR-5A for ir spectra, and Beckman DB for uv spectra. Gas chromatography was performed on a Perkin-Elmer 810 instrument equipped with a differential flame ionization detector on a 50 ft × 02 in. didecylphthalate capillary column. Thin layer chromatography carried out on silica gel (Merck PF$_{254}$). Elemental analyses were done by Galbraith Laboratories. Knoxville, Tenn. All melting points are corrected.

The results are summarized in Table I. The methiodide salts, **14** and **15** were isolated and the unreacted enamino ketone **12** was recovered by one of the three procedures (A, B, or C) described below. Recovered **12** was identified by tlc and ir spectral comparison with an authentic sample.

A. In Acetonitrile.—The reaction mixture was allowed to cool to room temperature and diluted with excess ether. After standing several days at −20°, the solution deposited 0.534 g (61%) of a mixture of **14** and **15** as colorless crystals, mp 110–160°. Evaporation of the mother liquor yielded 0.175 g (35%) of unreacted **12**.

B. In Nitrobenzene.—The reaction was conducted as above to yield 0.422 g (50%) of a crystalline mixture of **14** and **15**. The mother liquor was concentrated *in vacuo* to 15 ml before extracting with two 20-ml portions of 10% hydrochloric acid. The acid extract was rendered alkaline with 40% sodium hydroxide and extracted several times with dichloromethane. The organic layer was dried over anhydrous potassium carbonate and then evaporated to yield 0.175 g (35%) of **12**.

C. In Ethyl Acetate.—The reaction mixture deposited 0.107 g (12%) of a mixture of **14** and **15** as colorless crystals, mp 170–190°, during the course of 48 hr. Evaporation of the solvent after removing the precipitated product yielded 0.40 g (80%) of recovered **12**.

Reactions of Enamino Ketone (12, $n = 1$) with Methyl Iodide in Protic Solvents. General Method.—All reactions were carried out at 50 ± 2° for 48 hr in a nitrogen atmosphere using 0.50 g (2.6 mmol) of **12**, 5 ml of methyl iodide, and 15 ml of anhydrous solvent. The product was precipitated by adding 200 ml of anhydrous ether. The composition of the collected solid was qualitatively determined by ir and nmr spectroscopy. Quantitative estimation of the product composition was made from Beer–Lambert plots of A_s (334 mμ) *vs.* the concentration of hydriodide salt, **17** [334 mμ (ε 16,600)], in authentic mixtures of **17** and **14** [334 mμ (ε 12,600)] and **17** and **16** [334 mμ (ε 11,000)]. The method was based on differences in extinction coefficients (ε) for **14**, **16**, and **17** and was accurate to ±5%. The unreacted enamino ketone, which was recovered by evaporation of the mother liquor, was identified by tlc [ethyl acetate–hexane (3:7 v/v)] and ir spectral comparison with an authentic sample. The results are summarized in Table I.

A. In Methanol.—The reaction mixture deposited 0.626 g (72%) of a mixture of **14** and **17** as off-white needles: mp 117–127°; ir (CCl_4) 5.95 (s) and 6.40 (s) μ; λ_{max} 334 mμ. The nmr spectrum of this material exhibited a signal at τ 3.45 for the hydroxylic proton of **17** and a sharp singlet at 5.85 for the OCH_3 substituent in **14**. Evaporation of the mother liquor provided 100 mg (20%) of unreacted **12**.

B. In Ethanol.—From ethanol a total of 0.650 g (75%) of yellow crystals mp 130–157°, consisting of a mixture of the hydriodide salt, **17**, and the O-ethyl salt, **16**, was obtained. This material had ir (CCl_4) 6.00 (s) and 6.40 (s) μ; uv (EtOH) 334 mμ; nmr ($CDCl_3$) τ 4.35 (due to OH of **17**) and 5.57 and 8.55 ($J = 8$ Hz, OCH_2CH_3 of **16**).

C. In Propanol-2.—A duplicate of the experiment in methanol was carried out except that before dilution with ether the reaction mixture was distilled under reduced pressure (25 mm) at room temperature and the distillate (5.4 g) collected in a Dry Ice–acetone trap. Gas chromatographic analysis of the material in the cold trap showed that it contained isopropylmethyl ether, **24**. The latter compound was identified on the basis of the retention time which was identical with that for an authentic sample. The residue after distillation was diluted with ether to give 0.750 g (76%) of the hydriodide salt, **17**, as a yellow solid, mp 165–170°. The mixture melting point with an authentic sample showed no depression.

D. 2-Methyl-2-propanol.—The reaction was conducted as described above. Glpc analysis of the distillate showed that it contained *t*-butyl methyl ether, **21**. The residue after distillation was diluted with ethyl acetate and 0.450 g (56%) of the hydriodide salt, **17** was deposited on cooling. The filtrate was evaporated to yield 0.20 g (40%) of unreacted **12**.

Preparation of O-Methyl quinolizinium Perchlorate (14a).—A solution of 100 mg (0.3 mmol) of the O-methylquinolizinium iodide (**14**) in 2 ml of acetonitrile was treated with 1 ml of a solution of silver perchlorate (0.3 mmol/ml) in acetonitrile. The yellow precipitate of silver iodide which immediately formed was removed and washed several times with acetonitrile. The combined supernatant and washings were removed *in vacuo* at room temperature to give a colorless oil. This residual oil was dissolved in a very small amount of acetonitrile and diluted with ethyl acetate to provide 63 mg of the O-methylquinolizinium perchlorate, **14**, as colorless rods: mp 125–127°; ir ($CHCl_3$) 6.10 (m), 6.35 (s, broad), 6.90 (w), and 9.25 (s, broad) μ; uv (EtOH) 334 mμ (ε 11,800); nmr ($CDCl_3$) τ 5.92 (s, 3 H).

Anal. Calcd for $C_{13}H_{20}NO_5Cl$: C, 51.07; H, 6.59; N, 4.58. Found: C, 51.10; H, 6.40; N, 4.41.

1,2,3,4,4a,5,7,8-Octahydro-6-amino-9H-cyclopentano[*c*]quinolizinium Iodide (20).—A solution of 130 mg of **14** (or **16**) in 5 ml of acetonitrile was saturated with ammonia. The precipitate was collected and recrystallized from ether affording 97 mg (80%) of **20**: mp 202–205°; ir ($CHCl_3$) 2.98, 3.16, 6.05, and 6.20 μ; uv (EtOH) 348 mμ (20,200).

Anal. Calcd for $C_{12}H_{19}N_2I$: C, 45.31; H, 6.02; N, 8.81. Found: C, 45.54; H, 6.20; N, 8.90.

Reactions of Enamino Ketones Containing Six-, Seven-, and Eight-Membered Fused Rings (12, $n = 2$, 3, and 4) with Methyl Iodide in Acetonitrile. General Method.—A mixture of 0.50 g of enamino ketone (**12**, $n = 2$, 3, and 4), 5 ml of methyl iodide, and 15 ml of acetonitrile was heated in a nitrogen atmosphere at 50° for 48 hr. The methiodide salts (**25** and **26**) were precipitated by diluting the reaction mixture with ether and placing in a freezer for several days. The product composition was determined by ir and nmr spectroscopy, utilizing the spectral data shown in Table IV. No attempt was made to separate **25** and **26** from the product mixture. Quantitative estimation of the relative amounts of O- and C-methiodide salts was based on the integrated areas for the OCH_3 and CCH_3 singlets in the nmr spectra (Table IV). The relative areas of the two components were estimated by triangulation of their respective signals. The accuracy of this technique was found to be ±8% based on results from authentic mixtures of the known OCH_3 and CCH_3 salts, **14** and **15**.

TABLE IV

CHEMICAL SHIFTS ($CDCl_3$) OF CCH_3 (26) AND OCH_3 (25) PROTONS

n	τ, CCH_3 (**26**)	τ, OCH_3 (**25**)
2	8.69	5.85
3	8.64	5.92
4	7.80	...

Determination of pK_a Data.—The hydriodide salts[20] of enamino ketones **12** ($n = 1$, 2, and 3) (~1 mmol, weighed accurately) were dissolved in *ca.* 100–125 ml of water. This solution was titrated with standard 0.1046 *N* sodium hydroxide. All measurements were obtained in ambient temperature (~23°). Determination of the pH during the titration was made with a Beckman Zeromatic pH meter using calomel and glass electrodes. Duplicate values were obtained for each compound and the average values are shown in Table III. As a check of this method, the pK_a of aniline hydrochloride was found to be 4.63 (lit.[21] pK_a 4.59).

1,2,3,4,4a,5,6,8,9,10-Decahydro-7H-7-methoxylbenzo[*c*]quinolizinium Iodide (29).—A solution of 0.210 g of **13** and 0.25 ml of methyl iodide in 5 ml of acetonitrile was refluxed at 54° under argon for 5 hr. The solution was then poured into 150 ml of anhydrous ether. An oil formed which crystallized over a period of 24 hr yielding 0.246 g (69%) of **29**: mp 125–127°; uv (EtOH) 309 mμ; ir ($CHCl_3$) 6.37 μ; nmr ($CDCl_3$) τ 5.95 (s, 3 H, OCH_3).

Anal. Calcd for $C_{14}H_{22}NOI$: C, 48.43; H, 6.39; N, 4.03. Found: C, 48.35; H, 6.36; N, 3.99.

1,2,3,4,4a,5,6,8,9,10-Decahydro-7H-7-ethoxybenzo[*c*]quinolizinium Iodide (30).—A solution of 0.264 g of **13** and 0.27 ml of methyl iodide in 5 ml of acetonitrile was refluxed at 69° for 17.5 hr. The work-up procedure described above yielded 0.42 g (91%) of **30** as an oil: uv (EtOH) 310 mμ; ir (neat) 6.39 μ; nmr ($CDCl_3$) τ 5.64 (q, 2 H, OCH_2CH_3) and 8.60 (t, 3 H,

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(20) Prepared in a manner similar to that which afforded **17**. **12** ($n = 2$) had mp 265–267°; **12** ($n = 3$) had mp 259–262°.

(21) M. Kilpatrick and C. A. Arenberg, *ibid.*, **75**, 3812 (1953).

-OCH$_2$CH$_3$). No analytical results were sought for this compound since it would not crystallize even after prolonged standing.

1,2,3,4,4a,5,6,8,9,10-Decahydro-7H-7-aminobenzo[*c*]quinolizinium Iodide (31).—A saturated solution of ammonia in 10 ml of acetonitrile was added to the crude product **30** prepared from 0.4 g of **13** as described above. The acetonitrile was removed after 30 min yielding an oil. Crystallization from acetonitrile–ether gave 0.45 g (53%) of **31**: mp 164–165°; uv (EtOH) 328 mμ; ir (CHCl$_3$) 3.04, 3.19, and 6.01 μ; nmr (CDCl$_3$) τ 2.20 (s, 1 H, -NH$_2$) and 2.84 (s, 1 H, -NH$_2$).

Anal. Calcd for C$_{13}$H$_{21}$N$_2$I: C, 47.00; H, 6.37; N, 8.43. Found: C, 46.96; H, 6.30; N, 8.41.

Registry No.—Methyl iodide, 74-88-4; **12** (n = 1), 18121-40-9; **14,** 18650-05-0; **14a,** 19029-86-8; **15,** 18670-19-4; **16,** 18670-20-7; **17,** 18650-06-1; **20,** 18670-21-8; **25** (n = 2), 19039-34-0; **25** (n = 3), 19029-91-5; **26** (n = 2), 19029-92-6; **26** (n = 3), 19029-93-7; **26** (n = 4), 19029-94-8; **29,** 19029-95-9 **31,** 19029-96-0.

Mechanisms of Elimination Reactions. XXVI. Potassium *t*-Butoxide Promoted Dehydrochlorinations of the Isomeric Chlorodiphenylethenes[1]

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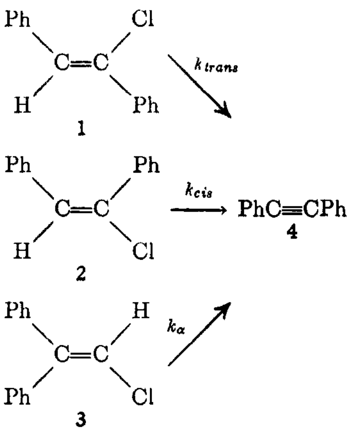
The isomeric chlorostilbenes have been subjected to potassium *t*-butoxide induced dehydrochlorination in *t*-butyl alcohol, in 5 *M* dimethyl sulfoxide in *t*-butyl alcohol, and in dimethyl sulfoxide (DMSO). The kinetics of these dehydrochlorinations were studied in the first two of these solvents, and competitive reactivities were measured in DMSO. In addition, the rates of potassium *t*-butoxide induced dehydrochlorination–rearrangement[3] of 2-chloro-1,1-diphenylethene in 5 *M* DMSO-*t*-BuOH and in DMSO[4] and a competition experiment with 1-chloro-*cis*-1,2-diphenylethene and 2-chloro-1,1-diphenylethene was performed in DMSO. The changes in reactivity ratios are discussed briefly.

A previous paper in this series[5] described the phenyllithium-induced dehydrochlorination of **1**, **2**, and **3**, all of which gave tolan (**4**) as product (Scheme I), and contrasted the relative rates of these processes, found to be $k_\alpha > k_{cis} > k_{trans}$, with the opposite order when sodium hydroxide in 92.6 wt% ethanol was used to effect the dehydrochlorination.[5b] Because of the large change in both the base strengths[6] and in the dielectric constants of the solvents,[8] the reversal in the relative rates seemed to deserve further investigation.

SCHEME I



Therefore, we undertook a study of the dehydrochlorination of the three isomers in which the base was to be held constant and the solvent was changed. The base chosen was potassium *t*-butoxide to avoid the formation of vinyl ethers as had been observed with ethoxide[3b] and also to make use of the capability to effect drastic changes in kinetic base strength[10] by changing solvent.

Experimental Section

Reagents and Solvents. *t*-Butyl Alcohol.—Eastman White Label *t*-butyl alcohol was allowed to react with cleansed potassium metal (10 g/l.) at reflux. The alcohol was then distilled into a flask containing molecular sieves (Linde, Type 4A). The alcohol was then redistilled through a 930 × 8 mm vacuum-jacketed, spiral-wire column under a stream of prepurified nitrogen (Mathieson). The material boiling at 76–77.5° (630 mm) was collected in a 4-l. serological bottle provided with a ground-glass stopper. The alcohol thus distilled had mp 25–25.5°, and 20 ml of alcohol would not decolorize 0.02 ml of Karl Fischer reagent. Immediately prior to use in the kinetic experiments, the alcohol was deoxygenated by evacuating while frozen and thawing under an atmosphere of nitrogen. A three-time repetition of this deoxygenation procedure seemed to be adequate for kinetic purposes as no color developed in the

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(1) Previous paper in series: S. J. Cristol and P. Pappas, *J. Org. Chem.*, **28,** 2066 (1963).

(2) This work was reported in the Ph.D. Dissertation of C. A. Whittemore, University of Colorado, 1963.

(3) (a) P. Fritsch, *Ann.*, **279,** 319 (1894); (b) W. P. Buttenburg, *ibid.*, **279,** 324 (1894); (c) H. Weichell, *ibid.*, **279,** 337 (1894).

(4) The kinetics of the dehydrochlorination of 2-chloro-1,1-diphenylethene for the system KO-*t*-Bu/*t*-BuOH have been reported by J. G. Pritchard and A. A. Bothner-By, *J. Phys. Chem.*, **64,** 1271 (1960).

(5) (a) S. J. Cristol and R. S. Bly, Jr., *J. Amer. Chem. Soc.*, **83,** 4027 (1961); (b) R. S. Bly, Jr., Ph.D. Thesis, Department of Chemistry, University of Colorado, 1958.

(6) The pK_A for benzene is variously reported as 36 to 40,[7] while those for water and ethanol are 14 and 18, respectively.

(7) (a) W. K. McEwen, *J. Amer. Chem. Soc.*, **58,** 1124 (1936); (b) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 19.

(8) Benzene, D. = 2.3;[9] ethanol, D. = 24.2.[9]

(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1958, p 193.

(10) Reference 7b, p 32.