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A NOVEL INTRAMOLECULAR CONDENSATION OF N-(2-CYANOMETHYLTRYPTOPHYL)PYRIDINIUM TOSYLATES

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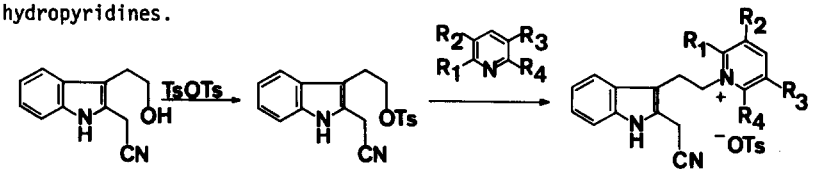
Condensations between pyridinium salts and enolate anions are of particular synthetic interest, since they constitute a useful means of constructing carbon-carbon bonds and yield dihydropyridines[2] which might provide unusual intermediates for further elaboration into alkaloid systems. There are several examples of intermolecular condensations between enolates and pyridinium salts,[3] as well as a related intramolecular condensation that proceeds in good yield under extremely mild conditions (aqueous $NaHCO_3$).[4] In the present work attention has been directed towards the cyclization of N-(2-cyanomethyltryptophyl)pyridinium salts, since salts of this type are known to exist as intramolecular charge-transfer (C-T) complexes,[5] and therefore, might be expected to cyclize readily to any one of several possible dihydropyridines.



2 1 3-7

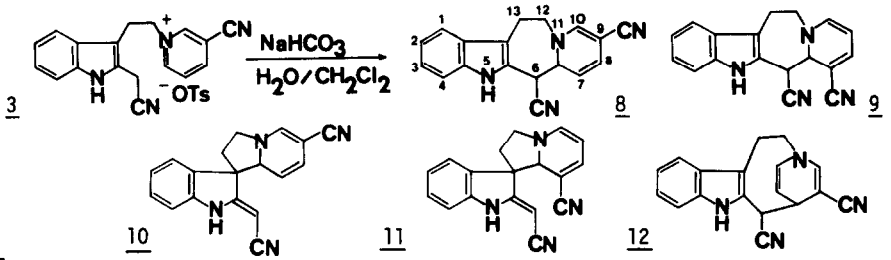
3 R_2 = CN; R_1, R_3, and R_4 = H (59%)
4 R_1 and R_4 = H; R_2 and R_3 = CO_2Me (77%)
5 R_2 and R_4 = H; R_1 and R_3 = CO_2Me (57%)
6 R_1 = D (93%); R_2 and R_4 = H; R_3 = CN
7 R_1 and R_4 = D (93%); R_2 and R_3 = CO_2Me

FIGURE 1.-

The desired enolate attack at the pyridinium nucleus is facilitated by electron withdrawing pyridinium substituents, and yet, these same substituents reduce the nucleophilicity of the pyridine nitrogen to such an extent that salt formation can be a very inefficient process. This difficulty can be circumvented by preparing the highly reactive 2-cyanomethyl-

tryptophyl tosylate (1) from the cyanoalcohol 2[6] using tosic anhydride,[7] and treating 1 with the appropriate pyridine (Fig. 1). The salts 3-7 are all colored substances displaying absorption spectra indicative of intramolecular C-T complexes in which the indole moiety is serving as the donor and the pyridinium moiety as the acceptor:[5,8] 3 (isopropyl alcohol) mp 125.5-127.5°, λ_{max}^{MeOH} 344 nm (light yellow); 4 (methanol-ethyl acetate) mp 205.4-205.8° (dec), λ_{max}^{MeOH} 360 nm (deep yellow); 5 (ethanol-water) mp 168.4-169.1°, λ_{max}^{MeOH} 347 and 430 nm (orange).

Each of these salts is rapidly transformed to dihydropyridines when treated with $NaHCO_3$. The dihydropyridines derived from the salts 3 and 4 are stable crystalline substances; whereas, those derived from 5 are quite unstable and were not characterized. If we neglect for the moment the possibility of isomers about the indole-derived cyano group, the cyclization of 3 might conceivably give rise to five dihydropyridine isomers (Fig. 2 8-12), and the symmetrically substituted 4 could give rise to three isomers. In fact the cyclization of 3 affords a single product in 90% yield, mp 201.1-201.3° (dec); m/e = 286; λ_{max}^{MeOH} 217 nm (ε 30,800), 242 (8000), 276 sh (7450), 284 (8000), 292 sh (7100), and 341 (3660). These data eliminate the α-indolenine structures 10 and 11 (λ_{max} = 310-320 nm),[9] and the linearly conjugated 1,2-dihydropyridine 9 (λ_{max} = 390 nm).[10] The 90 MHz nmr spectrum of this material exhibits the following set of four signals as confirmed by double resonance: $NC-CH_a-CH_b-CH_c=CH_d-$: H_a (δ) 4.11, d 1.8 Hz; H_b 4.86, complex; H_c 5.23, dd, 9.5 and 5.0 Hz; H_d 6.24, d, 9.5 Hz. This pattern might be attributed to either the $NC-CH_a-CH_b(N)-CH_c=CH_d-$ array in 8 or to the $NC-CH_a-CH_b-CH_c=CH_d-N$ array in 12. The former configuration was confirmed by the preparation of 6 from 2-deuterio-5-pyridinecarboxylic acid[11], and cyclization to the deuterated dihydropyridine lacking the signal at 4.86 δ. The small coupling constant between H_a and H_b (J = 1.8 Hz) indicates that 8 (6,6a,12,13-tetrahydro-5H-pyrido[1',2':1,2]azepino[4,5-b]indole-6,9-dicarbonitrile)[12] has the less hindered stereochemistry in which H_a and H_b are cis to each other (vide infra).



3 8 9 10 11 12

FIGURE 2.-

A similar examination of the cyclization of 4 and the dideuterated salt 7 has led to the isolation and structure proof of the cyano epimers of dimethyl 6-cyano-6,6a,12,13-tetrahydro-5H-pyrido[1',2':1,2]azepino[4,5-b]indole-7,9-dicarboxylate: the cis isomer 13 has mp 269.7-270.2° (dec); m/e = 377; λ_{max}^{MeOH} 221 nm (ε = 55,200), 284 (31,100), 291 sh (26,300), and 390 (6800); nmr (d_6-DMSO) (δ) 4.36, 1H (d, J = 2.3 Hz); 5.28, 1H (broad singlet); the trans isomer 14 has mp 273.5° (dec); m/e = 377; λ_{max}^{MeOH} 222 nm (ε = 44,600), 282 (27,700), 291 (20,700), and 378 (6400); nmr ($CDCl_3$ and d_6-DMSO) (δ) 4.61, 1H (d, J = 10Hz); 5.58, 1H (d, J = 10 Hz).

The dihydropyridine band in the UV spectrum of 14 (378 nm) is shifted to shorter wavelength relative to that of 13 (390 nm) due to the steric crowding between the cyano and the 7-carbomethoxy group which tends to force the carbomethoxy group out of conjugation with the dihydropyridine ring. This crowding is also evidenced by the facile epimerization of 14 to 13, and the absence of the reverse reaction under the same conditions. The cyclization of 4 proceeds through a readily detectable intermediate as illustrated in Fig. 3. The 360 nm band of 4 is extremely pH dependent. In methanolic HCl this band collapses to the usual featureless C-T envelope; whereas, in methanolic $NaHCO_3$ the intensity of this band is enhanced. In the presence of an excess of $NaHCO_3$ the intermediate species collapses smoothly to 13 as illustrated in Fig. 3. The intermediate may be isolated as an unstable oil by passing a solution of 4 through a column of silica gel eluting with $CHCl_3$:CH_3OH (90:10). This oil affords a mixture of 13 and 14 upon standing in a variety of solvents under neutral conditions.

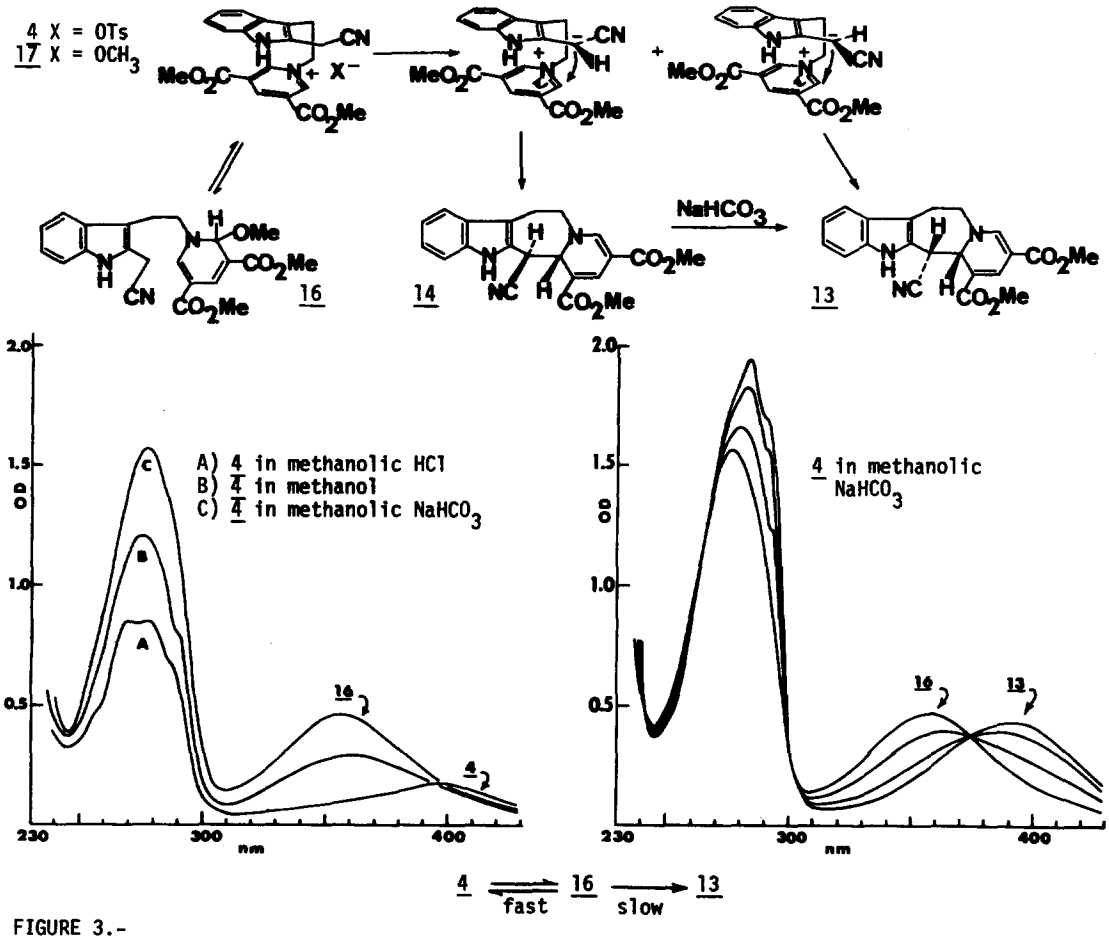


FIGURE 3.-

For example collapse of the intermediate at 40° in chloroform affords an 88% yield of 13 and 14 (13:14 = 56:44). This contrasts to the 40° methanolic $NaHCO_3$ cyclization of 4 which affords an 89% yield of 13 and 14 (13:14 = 95:5). Since this 360 nm substance does not provide a well defined nmr spectrum, it was not possible to establish its structure with certainty. Therefore, N-methyl-3,5-dicarbomethoxypyridinium tosylate (15) was prepared and examined. The UV absorption properties of 15 were very similiar to those of 4: λ_{max}^{MeOH} 352 nm (ε = 3840); $\lambda_{max}^{MeOH-NaHCO_3}$ 350 nm (ε = 8200); $\lambda_{max}^{MeOH-HCl}$ >300 nm (ε = 0). The substance giving rise to the 350 nm band could also be isolated as an unstable gelatinous oil by chromatography of 15 on silica gel ($CHCl_3$:CH_3OH - 90:10): nmr ($CDCl_3$) (δ) 3.04, 3H, s; 3.19, 3H, s; 3.90, 3H, s; 3.92, 3H, s; 6.01, 1H, s; 7.91, 1H, s; 8.02, 1H, s. These data indicate that this material is N-methyl-2-methoxy-3,5-dicarbomethoxy-1,2-dihydropyridine, and by analogy that the material which accumulates during the cyclization of 4 is most probably the related dihydropyridine 16. Possibly 16 is in equilibrium with the pyridinium methoxide 17 which would be expected to eliminate methanol to form the betaines shown in Fig. 3, and these in turn would collapse to 13 and 14. Whether or not the proposed transient betaines, which might be expected to exist as strong C-T complexes, have any influence upon the mode of this cyclization is not presently known. We are continuing to investigate the scope of these fascinating pyridinium cyclizations.

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11. Decarboxylation of 2,5- and 2,3-pyridinedicarboxylic acid in D_2O affords high yields of selectively labeled 2-deuterio-5-pyridinecarboxylic acid and 2-deuterio-3-pyridinecarboxylic acid respectively. Examples of the decarboxylation procedure to yield unlabeled pyridinecarboxylic acids are: K. Uda, A. Sakurai, and K. Sakabibara, Japan 20,555 (1965); Chem. Abstr., 64, 2096c (1966); J. Van de Kamp and G. C. Paulsen, Jr., Can. 435,865 (1946); Chem. Abstr., 40, 7238(6) (1946).
12. We are indebted to K. L. Loening of Chemical Abstracts Service, Columbus, Ohio, for providing the nomenclature of this compound.