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SOLVOLYTIC REARRANGEMENT OF THE TRYPTOPHYL SYSTEM

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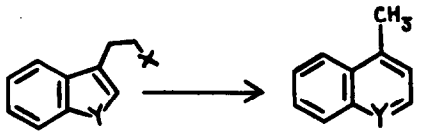
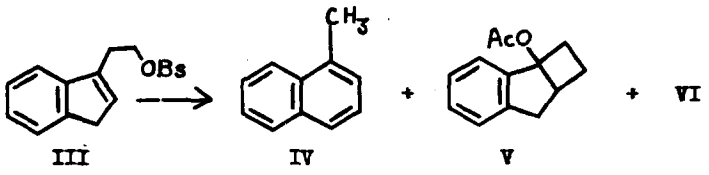
The facile solvolytic rearrangement of 2-(Δ^1-cyclopentenyl)-ethyl brosylate to the 3-methylenecyclohexyl system (50% in acetic acid)[3] led us to examine possible extensions of this type of reaction. In particular, the possibility of converting structures of type I to those of type II appeared intriguing. Acetolysis of



I II

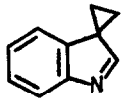
2-(3-indenyl)ethyl brosylate (III) (m.p. 57.5-58.5° dec.) (prepared from 2-(3-indenyl)ethanol[4]) was found to produce a small amount (8%) of 1-methylnaphthalene (IV) along with 51% 2,3-benzbicyclo-(3.2.0)hept-2-en-1-yl acetate (V) and 25% unrearranged 2-(3-indenyl)-ethyl acetate (VI). The remainder of the product is an as yet unidentified hydrocarbon. (The structure of V was assigned from IR and NMR data, fragmentation pattern of its mass spectrum, and analogy with similar reactions.[3])



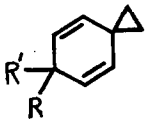
III IV V

The tryptophyl system (I, Y = NH) should be quite prone to ionization by neighboring participation, considering the nucleophilicity of the β-position of the indole ring. Acetolysis and ethanolysis of tryptophyl tosylate (VII) (m.p. 79-81° dec.) (prepared from tryptophol[5]) yielded only unrearranged tryptophyl derivatives, however. That participation does take place is indicated by the extreme reactivity of VII (Table I), and by the fact that the two carbons of the ethyl chain are completely equilibrated in the solvolysis product. Thus, acetolysis of α,α-dideuterotryptophyl tosylate yielded a mixture of equal parts of α,α-dideutero- and β,β-dideuterotryptophyl acetate. (NMR (CCl_4): identically sized singlets at 5.67 and 6.95 τ corresponding to an average of 1 proton at both the α- and β-positions of the ethyl chain.) Treating the tosylate with one equivalent of potassium t-butoxide in dry tetrahydrofuran, removing the solids by filtration under nitrogen, and concentrating the solution yielded a reactive oil identified as the spiro-indolenine (VIII) (6-aza-4,5-benzspiro(2.4)hepta-4,6-diene). The structure of VIII was confirmed by absence of NH stretching bands in the IR and an NMR spectrum exhibiting an A_2B_2 multiplet centered at 8.44 τ, corresponding to 4 protons. Assignment of these 4 protons to the cyclopropane ring in VIII is in excellent agreement with observed values of 8.3-8.8 τ for the cyclopropane protons of spiro compounds of

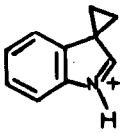
general structure IX.[6] Also supporting the structure of VIII is the fact that treatment with water or ethanol promptly yields the corresponding tryptophyl derivative. The rates of solvolysis of III, VII, and related compounds are presented in Table I.



VIII



IX



X

In light of the great reactivity of tryptophyl tosylate (ca. 10^4 times that of 2-(1-naphthyl)ethyl tosylate, a reasonable reference compound[7]) and the complete equilibration of the carbons in the ethyl chain in the products, it is clear that it solvolyzes in hydroxylic media entirely through Ar_1-3 participation. The reactivity of the indole ring in this respect probably exceeds that of any uncharged aromatic ring system investigated thus far. Failure of VII to undergo further rearrangement during solvolysis, comparable to that observed for III probably reflects both the stability of the aromatic pyrrole ring as opposed to the cyclopentadienyl ring in III and the expected stability of the indoleninium ion X. Further rearrangement of X would certainly involve structures of much higher energy. Treatment of tryptophyl derivatives and of VIII with a variety of lewis acids has thus far failed to produce products showing further rearrangement. While conversion of VII to a quinoline derivative by a carbonium ion pathway appears difficult, its reactivity and tendency to ionize by way of structure X are of obvious relevance to the synthesis and biochemistry of tryptophyl derivatives.[9]

TABLE I

Rates of Solvolysis of Sulfonate Esters[a]

Compound	Temp.	10^5k, sec.$^{-1}$ Ethanol[b]	10^5k, sec.$^{-1}$ Acetic Acid[c]
2-(Δ^1-cyclopentenyl)-ethyl brosylate	80°	7.75[d]	11.0[d]
2-(3-indenyl)ethyl brosylate	80°	5.86	0.471
2-(1-naphthyl)ethyl tosylate	80°	0.704	0.103
	100°	-	0.877
tryptophyl tosylate	25°	-	3.77
	35°	-	11.8
	40°	45.1	-
	45°	-	34.2
	50°	136	-

[a]Rate constants have an average error of about 2%. [b]Measured by a conductometric procedure. [c]Solutions were initially 0.03 M in sulfonate ester and 0.035 M in sodium acetate. [d]Data from ref. 3.

The solvolytic reactivity of III is considerably less than that of 2-(Δ^1-cyclopentenyl)ethyl brosylate[3] and this is mainly attributable to the lower ground-state energy of the conjugated double bond in III. The much larger fraction of condensed cyclobutane derivative formed from III during acetolysis is probably indicative of stabilization by conjugation with aromatic ring of the particular ion or ions leading to V. The high yield of V is another illustration of the utility of solvolytic cyclization in synthesis of

condensed cyclobutane structures, a point made recently by Hanack and Schneider.[10]

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7. While it has been shown that acetolysis of 2-(1-naphthyl)ethyl tosylate probably proceeds through a phenonium ion intermediate,[8] this obviously results in little rate enhancement. The actual rate of acetolysis is a little less than that of saturated primary aliphatic tosylates.

8. D. J. Cram and C. K. Dalton, J. Amer. Chem. Soc., 85, 1268 (1963).

9. Professor M. Julia of the Institut Pasteur, Paris, has informed us that several solvolytic or other nucleophilic displacement reactions on tryptophyl derivatives substituted in the ethyl chain yield rearranged products indicative of cationic intermediates analogous to X.

10. M. Hanack and H.-J. Schneider, Liebigs Ann. Chem., 686, 8 (1965); Angew. Chem., 76, 783 (1964).