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THE REACTIONS OF 2-(2-INDOLYL)ETHYL TOSYLATES WITH BASES, A NOVEL RING ENLARGEMENT REACTION OF INDOLE RING

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The chemistry of tryptophyl tosylates has been investigated in connection with the synthetic studies of the indole alkaloids (1). However, the reaction of 2-(2-indolyl)ethyl tosylates has not yet been studied. This paper deals with the reactions of these tosylates with the conjugate bases of ethyl cyano- and acetoacetates.

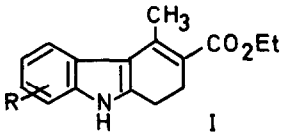
Ethyl 2-indolylacetate has been synthesized by Giuliano and Stein (2) and by Schindler (3). Ethyl esters of unsubstituted, 5-methoxy-, and 7-methoxy-2-indolylacetic acids were prepared by the former method and reduced with lithium aluminum hydride into the corresponding alcohols, which were in turn tosylated by the usual method. The structures of the tosylates were confirmed by the IR spectra (Table 1).

TABLE 1

2-(2-Indolyl)ethyl Tosylate		M.P. °C	ν_{max}^{Nujol} cm^{-1}	
			N-H	SO_2
Unsubstituted	$C_{17}H_{17}O_3NS$	114-116	3480	1340 1170 1160
5-Methoxy-	$C_{18}H_{19}O_4NS$	96-97	3440	1370 1180
7-Methoxy-		Oil	3440	1360 1190 1175

The reactions of the three tosylates with ethyl acetoacetate in the presence of sodium ethoxide in ethanol gave ethyl 4-methyl-1,2-dihydrocarbazole-3-carboxylates (I, R = H: $C_{16}H_{17}O_2N$, m.p. 162-163°; R = 6-Methoxy-: $C_{17}H_{19}O_3N$, m.p. 180-181°; R = 8-Methoxy-: $C_{17}H_{19}O_3N$, m.p. 164-165°, respectively). The identity of the ring system of the products is evident from the spectral data (Table 2). The dihydrocar-

bazole (I, R = H) obtained from the unsubstituted tosylate was dehydrogenated by melting with palladium-on-carbon and cinnamic acid, followed by hydrolysis with potassium hydroxide in boiling ethylene glycol and subsequent decarboxylation of the resulting acid by heating with copper powder in quinoline, giving 4-methylcarbazole, m.p. 114-117° (lit. m.p. 115-116° (4)), which was characterized as the picrate, m.p. 165° (lit. m.p. 160.5° (4)). The derivation into the carbazole derivative and the spectral data confirmed the structure I sufficiently.



I

TABLE 2

Compound I	λ_{max}^{EtOH} mμ (log ε)	ν_{max}^{Nujol} cm^{-1}	δ^{CDCl_3} ppm*				
		N-H C=O	$OCH_2\underline{CH_3}$	$\underline{CH_3}$**	$OC\underline{H_3}$	$OC\underline{H_2}Me$	NH
Unsubstd.	234 (4.38) 285 (3.96) 354 (4.13) 261 (3.88) 307 (3.85)	3248 1662	1.32^t	2.76^s		4.29^q	8.35^{bs}
6-Methoxy-	236 (4.28) 285 (4.10) 354 (4.15)	3295 1665	1.34^t	2.76^s	3.85^s	4.23^q	8.30^{bs}
8-Methoxy-	234 (4.45) 260 (4.09) 356 (4.21)	3300 1660	1.32^t	2.78^s	3.93^s	4.27^q	8.60^{bs}

* Signal multiplicities are abbreviated as s, bs, t, q, and m for singlet, broad singlet, triplet, quartet, and multiplet, respectively, through this paper. The signals for the aromatic protons are omitted.

**The singlet includes also the absorption for the four protons of the methylene groups at C-1 and C-2 in each product.

The reaction of 2-(2-indolyl)ethyl tosylate with ethyl cyanoacetate in the presence of sodium ethoxide in ethanol gave a compound, $C_{13}H_{10}ON_2$, m.p. 148-150°. This compound was deduced to be 2-cyano-1,2,3,4-tetrahydropyrido[1,2-a]indol-1-one (II) from the spectral data. Neither NH nor OH absorption was found in the IR and NMR spectra, whereas the β-proton signal of the indole nucleus was observed. λ_{max}^{EtOH} mμ (log ε): 243 (4.28), 248 (4.29), 301 (3.50); ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N), 1709 (C=O; $\nu_{C=O}$ of N-acetylindole: 1711 cm^{-1} (5)); δ^{CDCl_3} ppm: 2.47^m (3-C$\underline{H_2}$), 3.07^m (4-C$\underline{H_2}$), 3.88^q (2-C$\underline{H}$), 6.34^s (5-C$\underline{H}$), 7.2-7.5^m (7, 8, and 9-C$\underline{H}$'s), 8.30^m (6-C$\underline{H}$).

On the other hand, the reaction of 5- or 7-methoxylated tosylate with ethyl sodiocyanoacetate under the same condition as above provided a peculiar ring enlargement

reaction. The spectral data (Table 3) of the products assigned them the structure of methoxylated 2-cyanoethoxycarbonylmethylene-2,3,4,5-tetrahydro(1H)-1-benzazepines, $C_{16}H_{18}O_3N_2$ (III, R = 7-Methoxy-: m.p. 125-126°; R = 9-Methoxy-: m.p. 162-163°, respectively). Six-proton signals between 2.1 and 2.9 ppm were assigned to a trimethylene grouping since neither methylene nor methyl singlet was observed in each of the spectra. The IR as well as the low-field NH signal in the NMR spectra (6) showed the presence of an NH-hydrogen bonded ester group in both compounds.

TABLE 3

Compound III	λ_{max}^{EtOH} mμ (log ε)	ν_{max}^{Nujol} cm^{-1}	δ^{CDCl_3} ppm*				
		N-H C≡N C=O	$OCH_2\underline{CH_3}$	$(\underline{CH_2})_3$	$\underline{CH_3}O$	$O\underline{CH_2}Me$	$\underline{NH}$
7-Methoxy-	317 (4.44)	3200 2200 1667	1.35^{t}	$2.1\text{-}2.9^{m}$	3.78^{s}	4.29^{q}	11.11^{bs}
9-Methoxy-	317 (4.41)	3200 2200 1660	1.37^{t}	$2.1\ 2.9^{m}$	3.85^{s}	4.19^{q}	10.99^{bs}

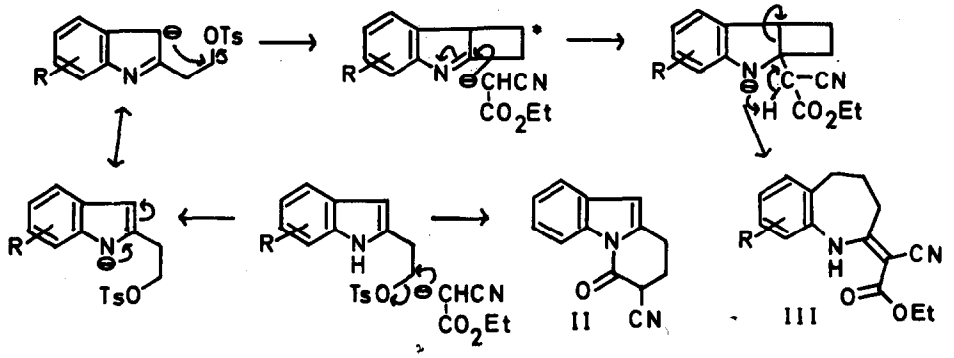
* The signals for the aromatic protons are neglected.

The structure of the products was verified by the synthesis of the 7-methoxyhydrobenzazepine (III, R = 7-Methoxy-) as follows. The Schmidt reaction of 6-methoxy-1-tetralone in trichloroacetic acid gave 7-methoxydihydrohomocarbostyril, $C_{11}H_{13}O_2N$, m.p. 158°, which was transformed into the corresponding imino ether by treatment with triethyloxonium fluoborate (7). The imino ether was allowed to react with ethyl sodiocyanoacetate (8) in dry benzene to give the desired hydrobenzazepine (III, R = 7-methoxy), in poor yield, along with ethyl γ-(2-amino-5-methoxyphenyl)butyrate, as a major product.

Incidentally, the reaction of the unsubstituted tosylate with ethyl sodiocyanoacetate was carried out in dimethyl sulfoxide. Rather surprisingly, the product was the unsubstituted hydrobenzazepine (III, R = H), $C_{15}H_{16}O_2N_2$, m.p. 110-111°. The structure was confirmed by the spectral data: λ_{max}^{EtOH} 310 mμ (log ε 4.10); ν_{max}^{Nujol} cm^{-1}: 3200 (N-H), 2200 (C≡N), 1670 (C=O); δ^{CDCl_3} ppm: 1.35^{t} ($OCH_2\underline{CH_3}$), $2.1\text{-}3.0^{m}$ ($(\underline{CH_2})_3$), 4.30^{q} ($O\underline{CH_2}CH_3$), $6.85\text{-}7.5^{m}$ (aromatic protons, 4H), 11.35^{bs} ($\underline{NH}$).

The formation of the compounds III may be explained as shown in the attached chart. The alkylation of the sodium derivatives or the Grignard derivatives of indoles are well known to give the N- and/or β-alkylated products (9). This is the first case of the postulation of a cyclobutanoindolenine intermediate, although the formation of a cyclobutane ring has been observed in the solvolysis of 2-(3-indenyl)ethyl brosylate

(1b). The N=C linkage of the indolenine system is susceptible to the nucleophilic addition (10). The ring opening of the cyclobutane ring may provide a sufficient driving force for the last step leading to the compounds III.



The compound I and II may be formed by the direct displacement of the tosyl group by the conjugate bases of ethyl aceto- or cyanoacetate, respectively; however, another possibility that these anions might attack the cyclobutanoindolenine intermediate at the site marked by an asterisk would not be excluded. The solvent effect observed in the dimethyl sulfoxide solution also remains inexplicable. The detailed interpretations in these respects will be presented in a later paper of this series.

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