

Structure and Properties of Products of the Conrad-Limpach Reaction Applied to 3-Aminocarbazoles

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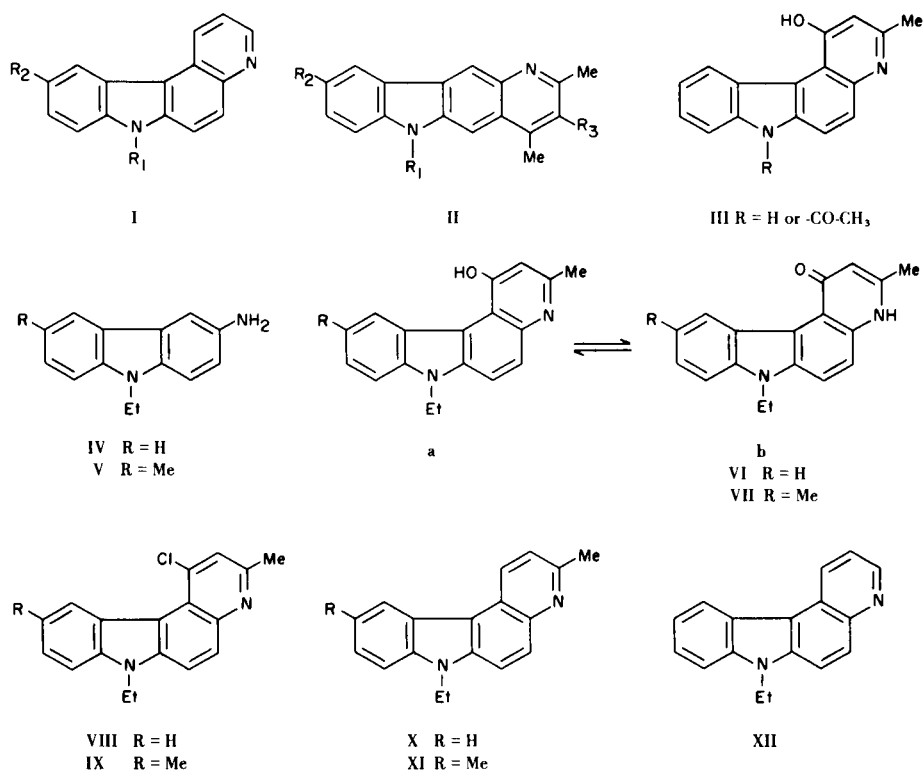
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In an earlier paper (1) we showed that 3-aminocarbazoles easily undergo Skraup and Combes-Beyer reactions and are convenient intermediates for the preparation of derivatives of 7*H*-pyrido[2,3-*c*]carbazole (I) and 6*H*-pyrido[3,2-*b*]carbazole (II). With a view to studying the behavior of aminocarbazoles toward other reagents and to acquiring new pyridocarbazole derivatives, we have now extended our investigation to the Conrad-Limpach synthesis (2), starting from 3-amino-9-ethylcarbazole (IV) and its 6-methyl homolog (V). The present paper reports our results.

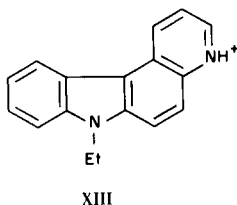
The amines IV and V underwent easy condensation with ethyl acetoacetate by heating in the presence of piperidine to yield ethyl 3-carbazolyl aminocrotonates, which could be readily cyclized by heating at 240° in paraffin medium. Cyclization followed the Marckwald

rule (3) and, as is the case with the Skraup reaction (1), led to angular compounds VI and VII; uv absorption and nmr spectra confirm these angular structures. Takanobu and Masaaki (4), who applied the Conrad-Limpach reaction to 3-aminocarbazole and its *N*-acetyl derivative, obtained compounds III and provided chemical confirmation of their angular structure, but did not concern themselves with the *tautomeric form* of their compounds; the studies we conducted of the chemical and physical properties of VI and VII have shown these last to exist preferentially (even in the solid state) in the form of quinolones (VIb and VIIb).

It is known that 2- and 4-hydroxyquinolines can undergo lactim-lactam tautomerism and exist both in the quinolol (lactim) and quinolone (lactam) form (5); in solution, a notable shift of this equilibrium occurs in favor



of the lactamic form, as Steck (6) demonstrated by his absorption spectra studies of several quinolols. In most cases, these quinolols-quinolones retain certain quinolic properties (5,6); but with our two compounds (VI and VII), even in the solid state we were unable to evidence their phenolic character; thus, they gave no coloration with ferric chloride and remained unchanged on distillation with zinc powder (7). Both chemically and physico-chemically also, VI and VII present the characteristics of quinolones. Their ir absorption spectra show a strong band in the 1620 cm^{-1} region characteristic of an amide carbonyl group (8) and out-of-band vibrations of amido NH groups in the 1580 cm^{-1} region. Like the cyclic amides, they reacted easily with phosphorous oxychloride (9,10) to furnish 1-chloro-7-ethyl-3-methyl-7H-pyrido[2,3-c]carbazoles (VIII and IX), which underwent basic hydrogenolysis in presence of Raney nickel (11) to give 7-ethyl-3-methyl-7H-pyrido[2,3-c]carbazole (X) and its methyl homolog (XI).



Study of the uv absorption spectra of these various compounds throws interesting light on the structures of VI and VII. From Figure 1, which shows the spectra of compounds VI and VIII, together with that of 7-ethyl-7H-pyrido[2,3-c]carbazole (XII) [obtained by Skraup

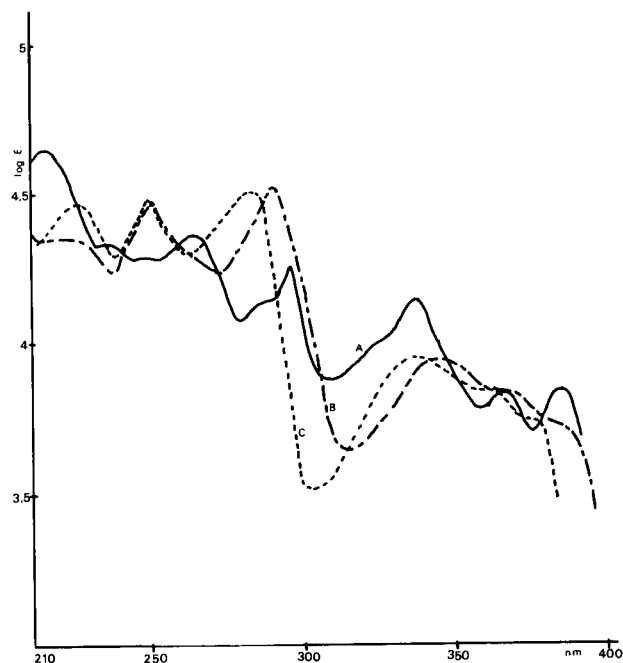


Figure 1. Uv spectra in ethanol of compounds: (VI) (A); (VIII) (B); (XII) (C).

synthesis, and whose structure was discussed in a previous paper (1)], it is seen that apart from the bathochromic shifts due to the Cl and Me substituents, the spectra of VIII and XII are almost identical, thus confirming the angular structure of VI and VII. However, the spectrum of VI is quite distinct from that of VIII; the difference observed in the number and position of the maxima are too

TABLE I

Uv Spectra of Derivatives of 7H-pyrido[2,3-c]carbazoles

Compound	Solvent	Principal bands: λ max nm log ϵ (in parentheses)					
		a	b	c	d	e	f
VI	Et	216 (4.66)	264 (4.37)	296 (4.26)	337 (4.55)	367 (3.84)	386 (3.84)
VI	HCl 0.01M in Et (a)	209 (4.62)	253 (4.59)	301 (4.40)	—————	359 (4.03)	—————
VI	NaOH 0.01M in Et	219 (4.45)	262 (4.46)	297 (4.31)	336 (4.10)	365 (3.77)	383 (3.98)
VII	Et	218 (4.64)	267 (4.34)	300 (4.23)	343 (4.19)	372 (3.82)	391 (3.78)
VIII	Et	226 (4.36)	251 (4.48)	291 (4.53)	344 (3.94)	369 (3.83)	392 (3.64)
X	Et	225 (4.53)	248 (4.51)	278 (4.54)	335 (4.02)	361 (3.87)	378 (3.78)
XII	Et	227 (4.46)	248 (4.49)	282 (4.52)	337 (3.96)	357 (3.85)	375 (3.75)
XII	HCl 0.01M in Et	218 (4.42)	253-60 (4.51)	303 (4.29)	—————	401 (3.95)	—————

(a) In this solution, there is a loss of fine structure that is especially pronounced in the region of the benzenoid transition bands; this effect is frequently observed in nitrogen heterocycles (12).

TABLE II

Chemical Shifts of Characteristic Protons (δ in ppm) from Me_4Si

Compound	11-H	NH
VI	multiplet 9.8	broad signal 11.58
VII	doublet 9.53	broad signal 11.5
XII	multiplet 8.34	

important to be ascribed to a mere substituent effect and are more probably due to a modification of the electronic structure of the quinolic nucleus in passing from compound VI to compound VIII. As is seen, Curve A (VI) shows two maxima at 216 and 337 nm that are fairly characteristic of γ -quinolones (6), and further, the general hypsochromic effect observed in the region of the benzenoid bands (210-300 nm) in A as compared with B can be explained by the loss of aromaticity brought about by the *pseudo*-quinonic form VIb. The absorption of VI at different pH, in hydrochloric ethanol at 0.01 M and in ethanolic sodium hydroxide at 0.01 M supports these observations: as Table I shows, there is no marked bathochromic effect significant of a quinolol form (6) whereas, for example, the spectrum of XII in acid medium presents, for the wavelengths toward 350 nm, a bathochromic shift of up to ~ 50 nm ascribable to the quinolinium ion XIII, which could be formed only in the case of a quinoline or quinolol structure, and not from a quinolone.

Lastly, nmr spectral data (Table II) for compounds VI and VII are also consistent with the structures proposed. The aromatic proton shows at 9.8 ppm for VI and 9.53 ppm for VII, respectively, a highly deshielded signal as compared with the aromatic envelope, corresponding to the 11-proton that is under the *peri* effect of the carbonyl group at the opposite angular summit, this effect being much more pronounced than in the case of an OH; in the spectrum of XII the 11-proton shows resonance only at 8.34 ppm. In addition, the broad signal in the weak regions (11.58 ppm for VI and 11.5 ppm for VII) is more representative of an amide NH than of a phenolic OH.

EXPERIMENTAL

Ir absorption spectra (potassium bromide) were recorded on a Perkin-Elmer 457 spectrometer; uv absorption spectra were measured with a Beckman spectrometer (model DB at double beam); nmr spectra were determined in DMSO or deuteriochloroform solutions with TMS as internal reference, on a Varian A 60 spectrometer.

7-Ethyl-3-methyl-1-oxo-1,4-dihydro-7H-pyrido[2,3-c]carbazole (VIb).

An ethanolic solution of 10 g. of 3-amino-9-ethylcarbazole and 6.8 g. of ethyl acetoacetate in presence of 1 drop of piperidine was heated under reflux for 24 hours, then maintained at room temperature for a further 24 hours. The solvent was removed by vacuum distillation and the crude product was taken up in paraffin oil and heated at 240° for 20 minutes. After cooling, the mixture was treated with petroleum ether and the precipitate obtained was dried and recrystallized, to form colorless microprisms (8.6 g.), m.p. 318° , from absolute ethanol.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$: C, 78.2; H, 5.8; N, 10.1. Found: C, 78.2; H, 5.7; N, 10.0.

Picrate: greenish yellow microprisms, m.p. 291° , from chlorobenzene.

Anal. Calcd. for $\text{C}_{24}\text{H}_{19}\text{N}_5\text{O}_8$: N, 13.8. Found: N, 13.6.

7-Ethyl-3,10-dimethyl-1-oxo-1,4-dihydro-7H-pyrido[2,3-c]carbazole (VIIb).

This compound, obtained from the amine V, as for VI and in good yield (67%), crystallized in colorless prisms, m.p. 324° , from absolute ethanol.

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$: C, 78.6; H, 6.2; N, 9.6. Found: C, 78.5; H, 6.3; N, 9.4.

Picrate: greenish yellow microprisms, m.p. 281° , from chlorobenzene.

Anal. Calcd. for $\text{C}_{25}\text{H}_{21}\text{N}_5\text{O}_8$: N, 13.5. Found: N, 13.3.

1-Chloro-7-ethyl-3-methyl-7H-pyrido[2,3-c]carbazole (VIII).

A mixture of 5 g. of compound VI and 20 ml. of phosphorus oxychloride was gently boiled for 2 hours, and after cooling, carefully poured on crushed ice and treated with ammonia to pH 9. The solid obtained was dried, washed thoroughly with water, and recrystallized in colorless microprisms (5.4 g.), m.p. 112° , from cyclohexane.

Anal. Calcd. for $\text{C}_{18}\text{H}_{15}\text{ClN}_2$: C, 73.3; H, 5.1; N, 9.5. Found: C, 73.3; H, 5.2; N, 9.3.

Picrate: yellow microprisms, m.p. 217° , from chlorobenzene.

Anal. Calcd. for $\text{C}_{24}\text{H}_{18}\text{ClN}_5\text{O}_7$: N, 13.4. Found: N, 13.2.

1-Chloro-7-ethyl-3,10-dimethyl-7H-pyrido[2,3-c]carbazole (IX).

This carbazole (90% yield), obtained from VII as for VIII, crystallized in colorless microprisms, m.p. 115° , from cyclohexane.

Anal. Calcd. for $\text{C}_{19}\text{H}_{17}\text{ClN}_2$: C, 74.0; H, 5.5; N, 9.1. Found: C, 73.9; H, 5.5; N, 9.0.

Picrate: yellow prisms, m.p. 240° , from chlorobenzene.

Anal. Calcd. for $\text{C}_{25}\text{H}_{20}\text{ClN}_5\text{O}_7$: N, 13.0. Found: N, 12.8.

7-Ethyl-3-methyl-7H-pyrido[2,3-c]carbazole (X).

A solution of 2 g. of compound VIII in alcoholic potassium hydroxide [(2 g.) in ethanol (300 ml.)] was treated with 20 g. of Raney nickel and kept at room temperature for 36 hours under magnetic stirring. The metal was then filtered and the solvent was removed by evaporation *in vacuo*. The solid obtained crystallized in colorless microprisms (1.45 g.), m.p. 122° , from cyclohexane.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2$: C, 83.0; H, 6.2; N, 10.8. Found: C, 83.0; H, 6.0; N, 10.6.

Picrate: yellow prisms, m.p. 229° , from chlorobenzene.

Anal. Calcd. for $\text{C}_{24}\text{H}_{19}\text{N}_5\text{O}_7$: N, 14.3. Found: N, 14.1.

7-Ethyl-3,10-dimethyl-7H-pyrido[2,3-c]carbazole (XI).

Obtained from compound IX as for X, this carbazole (95%

yield) crystallized in colorless microprisms, m.p. 120°, from cyclohexane.

Anal. Calcd. for C₁₉H₁₈N₂: C, 83.3; H, 6.6; N, 10.2. Found: C, 83.1; H, 6.6; N, 10.1.

Picrate: yellow microprisms, m.p. 257°, from chlorobenzene.

Anal. Calcd. for C₂₅H₂₁N₅O₇: N, 13.9. Found: N, 13.7.

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