

## Studies on Electrophilic Substitution Reactions of 3-Phenyl-cycl[3.2.2]azine\*

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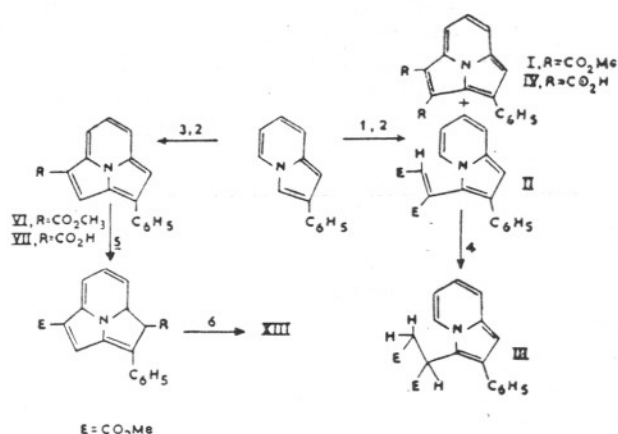
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Acetylation and formylation of 3-phenyl-cycl[3.2.2]azine derivatives, in the presence of Lewis acids, have been investigated. It has been found that the orientation of substitution in 2-carbomethoxy-3-phenyl-cycl[3.2.2]azine for these two reactions, under identical conditions, is different.

IN a projected study of substituted cycl[3.2.2]-azines as pharmacodynamic agents, it was found that very little information is available about the substitution reactions of 3-phenyl-cycl[3.2.2]azines; which prompted a study of their acetylation and formylation reactions, and the results are reported in this communication.

Boekelheide *et al.*<sup>1</sup> have described the synthesis of 1,2-dicarbomethoxy-3-phenyl-cycl[3.2.2]azine (I) by the reaction of 2-phenylpyrrocoline<sup>2</sup> and dimethyl acetylenedicarboxylate in the presence of Pd/C. We have observed that in this reaction in addition to I, a compound II, red needles, m.p. 141-2°, is also formed in the ratio of 4:1; which could be separated by column chromatography, and had the following spectral characteristics:  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1740, 1730; NMR (CDCl<sub>3</sub>) $\delta$ : 3.46 (s, 3H), 3.55 (s, 3H), 6.56 (*t* with further splitting, 1H, *J*=6, 2 Hz), 6.73 (s, 1H), 6.85 (*t* with further splitting 1H, *J*=7, 1 Hz), 7.26-7.66 (*m*, 7H); *m/e*: M<sup>+</sup> 335, 320 (M<sup>+</sup>-15), 276 (M<sup>+</sup>-59), 275 (M<sup>+</sup>-60), 244 (M<sup>+</sup>-91), 217 (M<sup>+</sup>-118). NaBH<sub>4</sub> reduction of II selectively reduced one double bond to give III, n.p. 144° (EtOH); NMR (CDCl<sub>3</sub>) $\delta$ : 2.61 (*q*, 1H, *J*=18, 4 Hz), 3.61 (*q* two arms of which were merged with OCH<sub>3</sub>-protons, *J*=18, 10 Hz), 3.70 (s, 3H), 3.78 (s, 3H), 5.03 (*q*, *J*=10, 4 Hz), 6.50-8.33 (*m*, 10H). The data presented above conveniently fit in structures II and III for the compounds.

I on basic hydrolysis yielded the diacid IV which on pyrolysis furnished a monoacid V, m.p. 184-85° (EtOH-H<sub>2</sub>O);  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1675. V was not identical with the monoacid VII, obtained by the reaction of methyl propiolate and 2-phenylpyrrocoline in the presence of Pd/C followed by basic hydrolysis. From the mechanism of addition of methyl propiolate in cycloadditions<sup>3-7</sup>, it is certain that the structure of VI is as shown in the formula. Therefore, V must have the carboxyl group at position-2, and during decarboxylation of IV the carboxyl group at position-1 has been lost. From MO calculations on cycl[3.2.2]azines<sup>8</sup> position-1 is considered to have a higher electron density than position-2. However our results on decarboxylation are contrary to this and it appears that in 3-phenyl-cycl[3.2.2]azine position-1 has lower electron density than 2,

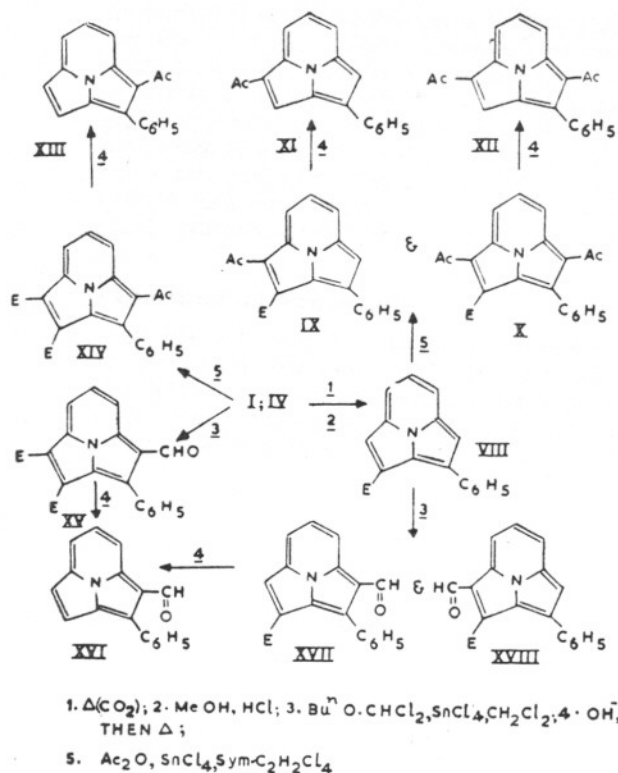


- E = CO<sub>2</sub>Me  
1. MeO<sub>2</sub>C-C≡C-CO<sub>2</sub>Me, Pd-C, Tol, 3-HC≡C-CO<sub>2</sub>Me  
4. NaBH<sub>4</sub>, MeOH;  
5. Ac<sub>2</sub>O, SnCl<sub>4</sub>, Sym-C<sub>2</sub>H<sub>2</sub>Cl<sub>4</sub>·OH<sup>-</sup>, THEN Δ

since in aromatic systems decarboxylation is more facile at position of lower electron density. V on treatment with MeOH/HCl gave methyl ester VIII, m.p. 60° (EtOH);  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1740.

VIII on treatment with Ac<sub>2</sub>O/SnCl<sub>4</sub> in sym-C<sub>2</sub>H<sub>2</sub>Cl<sub>4</sub> gave a mixture of two compounds IX and X, which were separated by chromatography on silica gel-G column using C<sub>6</sub>H<sub>6</sub> and CHCl<sub>3</sub> as eluants. The less polar compound IX, m.p. 146-7° (C<sub>6</sub>H<sub>6</sub>-hexane) contains one acetyl group;  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1750, 1660;  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 245, 266, 339; NMR (CDCl<sub>3</sub>) $\delta$ : 2.75 (s, 3H), 3.95 (s, 3H), 7.30-7.86 (*m*, 8H), 8.26 (*q*, 1H, *J*=7.5, 3 Hz); *m/e*: M<sup>+</sup> 317, 303 (M<sup>+</sup>-CH<sub>3</sub>), 302 (M<sup>+</sup>-CH<sub>3</sub>), 286 (M<sup>+</sup>-OCH<sub>3</sub>), 272 (M<sup>+</sup>-HCO<sub>2</sub>), 215 (M<sup>+</sup>-C<sub>8</sub>H<sub>6</sub>), 151 (M<sup>+</sup>-C<sub>8</sub>H<sub>6</sub>-C<sub>3</sub>H<sub>4</sub>). On hydrolysis and decarboxylation IX gave a monoacetyl compound XI, m.p. 106° (hexane);  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1640;  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 241, 267, 297, 336; NMR (CDCl<sub>3</sub>) $\delta$ : 2.76 (s, 3H), 7.35-8.25 (*m*, 9H), 8.43 (*q*, 1H, *J*=8, 4 Hz), different from XIII, m.p. 87-8° (hexane);  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1625;  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 248, 265, 286, 317; NMR (CDCl<sub>3</sub>) $\delta$ : 2.41 (s, 3H), 7.33-8.03 (*m*, 9H), 8.53 (*q*, 1H, *J*=6, 3 Hz), obtained by same series of reactions on VI. VI can be acetylated only in position 4 and the acetyl compound obtained after decarboxylation must be 3-phenyl-4-acetyl-cycl[3.2.2]azine (XIII) and IX, therefore, must be 1-acetyl-

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2-carbomethoxy-3-phenyl-cycl[3.2.2]azine\*. X, the more polar compound, m.p.  $156^\circ$  ( $\text{C}_6\text{H}_6$ );  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1750, 1670 (broad);  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 241, 276, 330; NMR ( $\text{CDCl}_3$ ) $\delta$ : 2.23 (s, 3H), 2.75 (s, 3H), 3.56 (s, 3H), 7.58 (s, 5H), 8.00 (t, 1H,  $J=8$  Hz), 8.56 (d, 1H,  $J=7$  Hz), 8.43 (d, 1H,  $J=7$  Hz), contains two acetyl groups. As the 3-phenyl group appeared as a sharp singlet in the NMR, the second acetyl group must also be in the cycl[3.2.2]azine ring, and X, therefore, is 1,4-diacetyl-2-carbomethoxy-3-phenyl-cycl[3.2.2]azine. On decarbomethoxylation X yielded XII, m.p.  $160^\circ$  (hexane);  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1660 (broad); NMR ( $\text{CDCl}_3$ ) $\delta$ : 2.38 (s, 3H), 2.70 (s, 3H), 7.50-7.83 (m, 5H), 7.93 (s, 1H), 8.05 (d, 1H,  $J=7$  Hz), 8.46 (d, 2H,  $J=7$  Hz).

I on acetylation, under similar conditions, furnished 1,2-dicarbomethoxy-3-phenyl-4-acetyl-cycl[3.2.2]azine (XIV), m.p.  $161^\circ$  (EtOH);  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1750, 1710, 1700, 1650;  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 267, 273, 325; NMR ( $\text{CDCl}_3$ ) $\delta$ : 2.25 (s, 3H), 3.63 (s, 3H), 4.01 (s, 3H), 7.56 (s, 5H), 7.96 (t, 1H,  $J=8$  Hz), 8.45 (t with finer splitting, 2H,  $J=8.5, 1$  Hz). XIV after removal of ester groups yielded a monoacetyl compound, identical with XIII, confirming the structure assigned to it above. XIII forms an oxime XIX, m.p.  $163^\circ$  (EtOH),  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3100 (broad), 1610, but does not form Schiff's base.

I on formylation using dichloromethyl *n*-butyl ether and  $\text{SnCl}_4$  (ref. 9), yielded 1,2-dicarbomethoxy-3-phenyl-4-formyl-cycl[3.2.2]azine (XV), m.p.  $146^\circ$  (MeOH);  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 2820, 1730, 1700, 1680, 1650;  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 245 (shoulder), 275, 330; NMR ( $\text{CDCl}_3$ )

\*The marked shielding of C-CH<sub>3</sub> signal (2.41 $\delta$ ), due to

adjacent phenyl ring, in the NMR spectrum of XIII and the appearance at the usual position of these protons (2.76 $\delta$ ) in the case of XI, supports the above assigned structures.

$\delta$ : 3.80 (s, 3H), 4.03 (s, 3H), 7.43-7.83 (m, 5H), 8.06 (t, 1H,  $J=7$  Hz), 8.53 (t, 2H,  $J=8$  Hz), 10.26 (s, 1H). Removal of ester groups from XV, yielded XVI, m.p.  $142^\circ$  (hexane);  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 2820, 1680, 1650.

Formylation of VIII, under identical conditions gave a mixture of two monoformylated products XVII and XVIII, which were separated by chromatography over neutral  $\text{Al}_2\text{O}_3$  column, using  $\text{C}_6\text{H}_6$  and  $\text{CHCl}_3$  as eluants. The less polar compound XVII, the major product, m.p.  $156^\circ$  ( $\text{C}_6\text{H}_6$ -hexane); NMR ( $\text{CDCl}_3$ ) $\delta$ : 3.70 (s, 3H), 7.50-7.90 (m, 5H), 8.00-8.20 (m, 3H), 8.71 (q, 1H,  $J=7, 2$  Hz), 10.21 (s, 1H), on decarbomethoxylation gave a monoformyl compound identical with XVI and is thus 4-formyl derivative of VIII. The more polar compound XVIII, m.p.  $180^\circ$  ( $\text{C}_6\text{H}_6$ );  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1730, 1640, 1620; NMR ( $\text{CDCl}_3$ ) $\delta$ : 3.78 (s, 3H), 7.50-8.11 (m, 8H), 8.70 (q, 1H,  $J=6, 4$  Hz), 10.91 (s, 1H) must, therefore, be the 1-formyl derivative.

XV on reacting with  $\text{C}_2\text{H}_5\text{NO}_2, \text{NH}_4\text{OAc}/\text{AcOH}$  gave a mixture of three compounds, which were separated by chromatography over neutral  $\text{Al}_2\text{O}_3$  column and two of these could be characterized. Elution with  $\text{C}_6\text{H}_6$  furnished XX, m.p.  $181-2^\circ$  ( $\text{C}_6\text{H}_6$ );  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1745, 1720, 1640, 1530, 1350; while elution with  $\text{CHCl}_3$  gave XXI, m.p.  $143-4^\circ$  (EtOH);  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1740, 1720, 2240. Further elution of column with MeOH yielded an unstable, highly insoluble compound which could not be characterized.

The NMR spectra of the compounds were in agreement with the structures assigned. There are, however, a few special features of the NMR spectra, which need comment. 3-Phenyl group could shield the *ortho* CO-CH<sub>3</sub> or CO-H signals, which was relatively more marked in 2-carbomethoxy compounds (X, XIV, XV and XVII), suggesting that with a *peri* carbomethoxy group the phenyl ring can be accommodated only by taking a position perpendicular to the plane of the molecule, thus causing marked deshielding of the O-C-CH<sub>3</sub> or C-H

protons. This fact could be used for deciding the position of the substituents in the molecule. In compounds having an acetyl, formyl or carbomethoxy group in positions 1 and/or 4 the *peri* protons of the pyridine ring were deshielded; in compounds having one such substituent, the *peri* proton appeared as a quartet, with  $J$  values varying from 2.3-5 and 5-8 Hz. This could be due to an *o*-coupling of 5-8 Hz and a *m*-coupling of 2-3.5 Hz, the latter appears abnormally high. The possibility of this quartet being due to a three proton spin system cannot at present be ruled out, and is being investigated. The structure of a typical quartet of XVI in its NMR is shown in Fig. 1. In cases where substituents were present in both positions-1 and 4, the signal for *peri* protons-5 and 7 was a triplet, appeared to

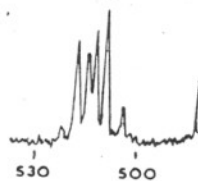


Fig. 1 — Structure of the typical quartet in the NMR of XVI

be formed from two overlapping doublets of  $J$  varying from 7-8 Hz. These couplings of this triplet could be discerned in the 6-H signal, which appeared relatively upfield as a triplet. The signal for phenyl group appeared as a multiplet in every case except for compounds X and XIV, which had an *o*-acetyl and a *peri* carbomethoxy group. We have not been able to find any special reason for the phenyl aromatic protons appearing as a singlet in these two cases.

#### Experimental Procedure

All the compounds have been routinely checked by elemental analysis, TLC, IR, UV and NMR. The NMR spectra were recorded on Varian A60D model, using TMS as an internal standard, and the chemical shift values are expressed in  $\delta$  units.

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