

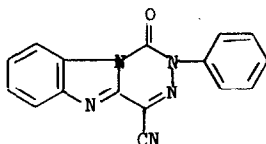
THE SYNTHESIS OF AN *as*-TRIAZINOBENZIMIDAZOLE BY OXIDATIVE CYCLIZATION

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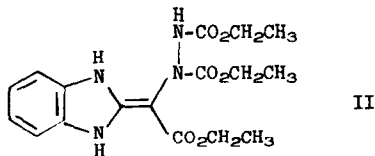
A recent report (1) on the synthesis of 1-oxo-2-phenyl-1,2-dihydro-(*as*-triazino) [5,4-*a*] benzimidazole carbonitrile (I), prompts us to report our novel synthesis of this ring system,



I

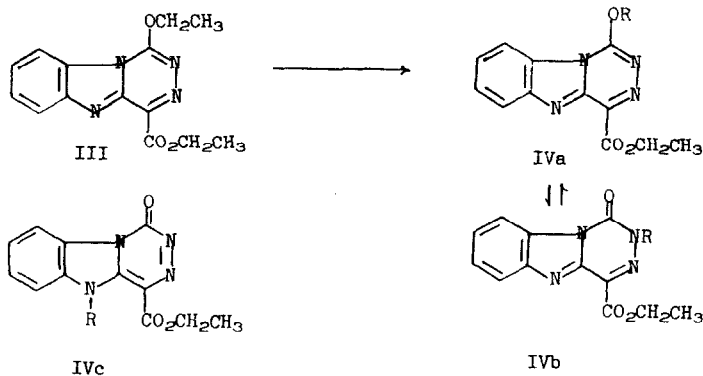
which heretofore had not been described.

Ethyl-2-benzimidazole acetic ester (2) in methylene chloride reacted exothermically with a molar equivalent of diethyl-azo-bis-carboxylate. After reflux for one hour to complete reaction, the mixture was filtered through silica gel. Elution by 5% methanol in methylene chloride gave a solid which was recrystallized from ether to yield II (70%, m.p. 128-130°C) (3).

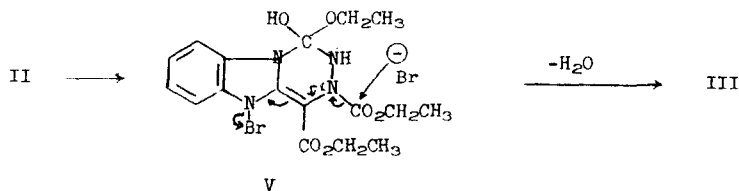


II

This tautomer is preferred over the benzimidazole form on the basis of the U.V. spectrum [ $\lambda_{\max}$  323 m $\mu$  ( $\epsilon$ , 14,450)] and I.R. spectrum (ester C=O;  $\nu_{\max}$  Nujol 1685  $\text{cm}^{-1}$ ). A solution in methylene chloride of II containing two molar equivalents of Hünig base (diisopropylethylamine) was cooled in ice and one equivalent of bromine added dropwise with stirring. Immediate work up gave a gum which on standing with ethanol gave crystals III (40%, m.p. 154-5°).

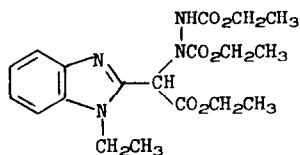


The structure of III was immediately apparent from the elemental analysis and the nmr spectrum which showed two types of O-ethyl function and four aromatic protons. The presence of an imido ether function was further substantiated by mild acid hydrolysis (50% aq. acetic acid, 4 hrs. steam bath) to IV. (R=H) [60%; m.p. 240-2° (IVb ex EtOH), m.p. 243-4° (IVa ex D.M.F.)]. Mechanistically the formation of III involves an intermediate such as V where



an imidazole nitrogen is added onto the terminal carbethoxy group. This type of compound has been postulated as being the product from ethanolysis of an appropriate chloro-as-triazine (4). The unusual feature here is loss of water instead of loss of ethanol and we will comment further on this phenomenon in our full paper. The hydrolysis product IV (R=H), (which may also be obtained directly from II by use of crude material and oxidizing at room temperature) is completely enolized in aprotic solvents. Crystallization from D.M.F. gives a product with a single carbonyl group in the I.R. spectrum ( $\nu_{\max}^{\text{Nujol}} 1725 \text{ cm}^{-1}$ ), which we assign structure IVa (R=H), while from ethanol one obtains a compound (IVb) with two peaks ( $\nu_{\max}^{\text{Nujol}} 1720, 1735 \text{ cm}^{-1}$ ). Both compounds on solution in acetonitrile give identical I.R. spectra, with a single carbonyl group. This type of enolization has been observed previously in 3,6-

pyridazinediones (5) and compound IV behaves more like this class of compound than as an *as*-triazine-3-one. Furthermore this observation is in keeping with the generalization developed by Katritzky (6) that amides are prone to enolize when the nitrogen is bonded to an atom with available lone pair electrons. Treatment of IV in methylene chloride containing the Hünig base with acetyl chloride yielded an O-acetyl compound (IVa, R = COCH<sub>3</sub>; 90%, m.p. 150-151°C,  $\nu_{\text{max}}^{\text{Nujol}}$  1800 cm<sup>-1</sup>). Alkylation both in ethanol (EtI|NaOEt) and D.M.F. (EtI|NaH) however, yielded the same N-alkyl compound (IVb, R = CH<sub>2</sub>CH<sub>3</sub>, 80%, m.p. 161-162°C,  $\nu_{\text{max}}^{\text{Nujol}}$  1715, 1735 cm<sup>-1</sup>). While the spectral evidence favored IVb, (R = CH<sub>2</sub>CH<sub>3</sub>) for the structure of this N-alkylated material, we undertook to confirm it, by synthesis of the isomer IVc, (R = CH<sub>2</sub>CH<sub>2</sub>). Using ethyl sulfate in place of methyl sulfate in the procedure for 1-methyl-2-cyanomethyl-benzimidazole (7), we obtained a crystalline N-ethyl compound (m.p. 156-157°C). Ethanolysis by refluxing ethanolic HCl yielded ethyl-1-ethyl-2-benzimidazole acetic ester (b.p. 151-153° | 0.4 mm). Reaction of this ester with diethyl-azo-bis-carboxylate in refluxing methylene chloride yielded, more slowly than the unsubstituted case, a crystalline product VI (80%, m.p. 82-84°C).



VI

Interestingly this compound is exclusively the benzimidazole tautomer. The U.V. spectrum being very similar to the starting ester [ $\lambda_{\text{max}}^{\text{MeOH}}$  258, 270, 277, 285 m $\mu$  (7,700), (7,010) (8,040) (6,980)] and the I.R. spectrum also shows a "normal" ester carbonyl (1735 cm<sup>-1</sup>). Reaction of VI with bromine in methylene chloride and the Hünig base, yielded a gum which on trituration with ethanol gave a small amount of crystalline material IVc (R = CH<sub>2</sub>CH<sub>3</sub>) (1% yield, m.p. 224-225°C). The structure of this material was confirmed by the nmr spectrum (2 types of ethyl, 4 aromatic protons) which closely resembled that of IVb (R = CH<sub>2</sub>CH<sub>3</sub>). The U.V. and I.R. spectra were however quite dissimilar, in a way reminiscent of the differences between II and VI. Thus IVc (R = CH<sub>2</sub>CH<sub>3</sub>) had a long wave length maximum

[(359  $\mu$  (11,750)], compared to IVb (R = CH<sub>2</sub>CH<sub>3</sub>) [(326  $\mu$  (8,550)]. The ester carbonyl was "abnormal" ( $\nu_{\max}^{\text{Nujol}}$  1675 cm<sup>-1</sup>) compared to a normal one ( $\nu_{\max}^{\text{Nujol}}$  1735 cm<sup>-1</sup>) in IVb (R = CH<sub>2</sub>CH<sub>3</sub>). From these observations we are confident that in the tautomeric equilibrium of IV (R = H), structure IVc (R = H) is not present to an extent detectable by U.V. or I.R. methods.

#### Acknowledgment

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