Application of a Thermal Rearrangement Reaction to Questions of Structure of Condensed Dihydrodiazepinones: The Reaction of 2,3-Diaminopyridine with Ethyl Benzoylacetate (1,2)

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Dedicated to Professor Allan R. Day

The condensation of an unsymmetrical aromatic diamine with a β-ketoester can afford two theoretically possible dihydrodiazepinone products, differentiation between which is, at best, difficult and laborious. A recently described (3) rearrangement reaction, whereby dihydrodiazepinones are thermally converted into N-substituted imidazolones, has now been applied to the elucidation of structures of ambiguous diazepinone derivatives. By means of the thermal rearrangement method, the diazepinone derivative resulting from the reaction of 2,3-diaminopyridine and ethyl benzoylacetate, for which structures 1a and 1b are equally plausible, has been definitively characterized as the 2-phenyl-4-one compound, 1a.

We have recently described the facile rearrangement of condensed dihydro-1,4-diazepinones into N-alkenylimidazolones (3). The ring contraction is brought about solely by the action of heat and occurs providing the endocyclic double bond exists as, or can be tautomerized into, an azomethine linkage. From a mechanistic point of view,
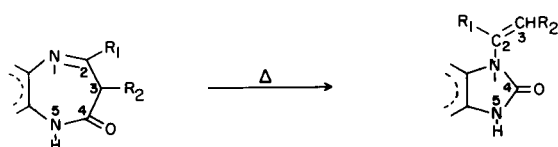

the reaction appears to be the first example of a [1,3]-sigmatropic shift of an acyl carbon to nitrogen, occurring, in this instance, with nonobservable inversion of the migrating carbonyl group (3,4). However, the reaction is of interest also from a practical standpoint in that it provides a convenient and simple method for characterizing condensed dihydrodiazepinones of ambiguous structure.

The condensation of an unsymmetrical aromatic diamine with a β-ketoester is inherently complicated by the possible formation of isomeric dihydrodiazepinone products. Some reactions lead to the formation of one isomeric diazepinone exclusively, while other reactions afford mixtures, in various proportions, of the two theoretically possible diazepinone products. Determination of the correct structure for a given diazepinone product from such a reaction has heretofore been a difficult and laborious, and, in some instances, an impossible task. The above mentioned thermal conversion of diazepinones into imidazolones now permits the assignment of correct structures to ambiguous diazepinone products through the knowledge that the N^1-C^2 bond of the diazepinone is not cleaved during the course of the rearrangement reaction (3). Thus, the structure of a condensed dihydrodiazepinone can be definitively determined by establishing the structure of its thermal rearrangement product, a much easier chemical problem to solve. We should like here to illustrate one application of this method, specifically as it applies to the structure of the diazepinone resulting from the reaction of 2,3-diaminopyridine with ethyl benzoylacetate.

The reaction of 2,3-diaminopyridine and ethyl benzoylacetate was first reported in a communication in 1964 (5). Avoiding the question of alternate possibilities of cyclization, the authors arbitrarily assigned to their product the diazepinone structure 1a. No evidence was given in support of the structure assignment.

Regardless of the exact mechanism by which this diazepinone is formed during the condensation reaction, the assignment of structure 1a implies condensation of the keto-carbonyl function of the β-ketoester with the more basic 3-amino group of the diamine, whereas the alternate structure 1b implies reaction of the carbethoxy function at this amino group. Although, as we have shown (6), the reaction of 2,3-diaminopyridine with ethyl acetoacetate in hot xylene affords that diazepinone (7) consistent with a crotonate intermediate, we have also observed (8) that, under identical conditions, the reaction of 4,5-diaminopyrimidine with ethyl acetoacetate yields as the major product the diazepine derivative consistent with an acetoacetamide intermediate, involving the more basic 5-amino function of the pyrimidinediamine. These and other
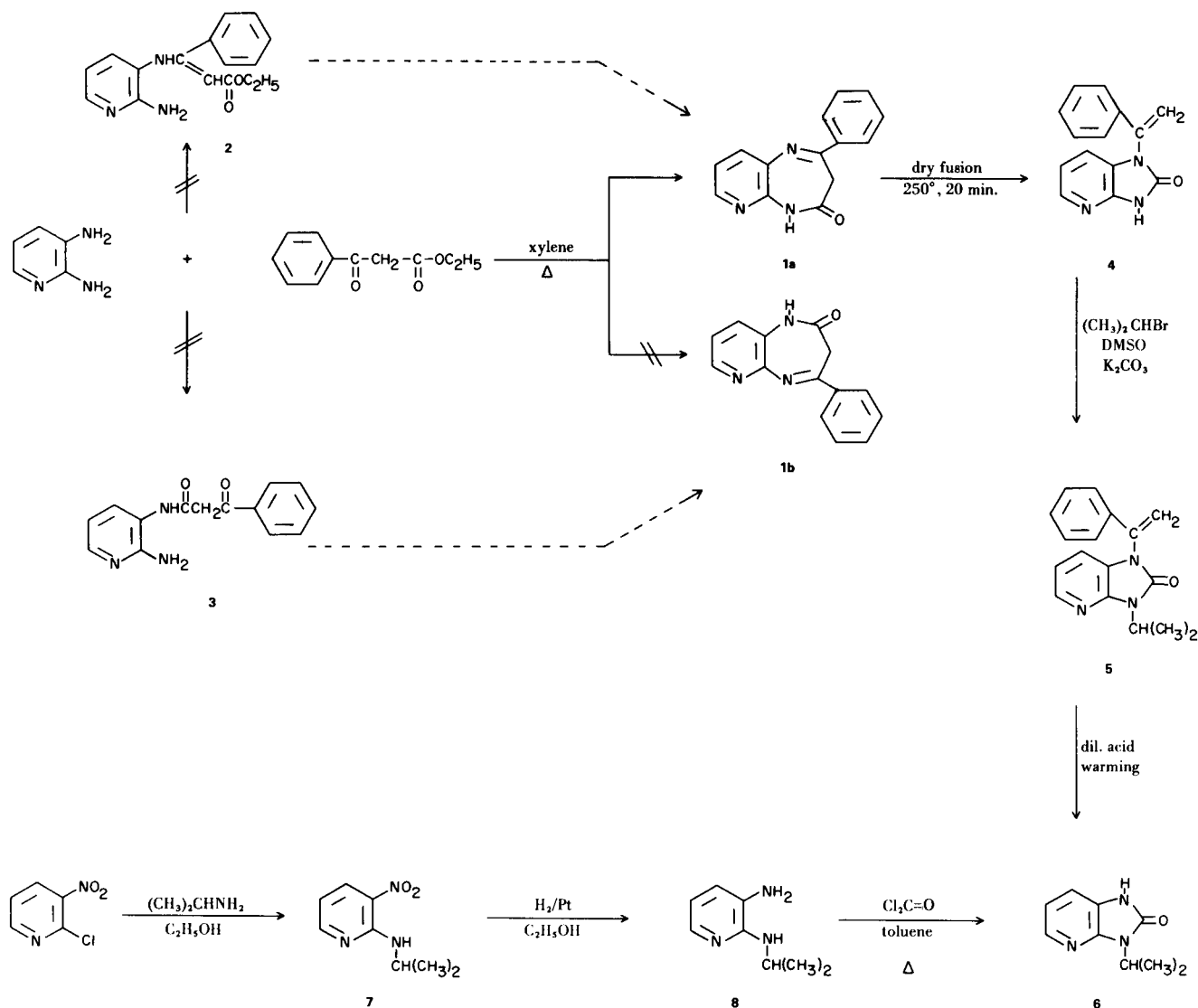
results, as yet unpublished, indicate a complete lack of predictability as to the mode of cyclization of a β-keto-ester with an aromatic diamine. We therefore felt that a rigorous proof of structure of the 2,3-diaminopyridine-ethyl benzoylacetate reaction product was required.

Condensation of 2,3-diaminopyridine and ethyl benzoylacetate in boiling xylene, in approximation of the incompletely defined conditions given by Barchet and Merz (5), afforded a diazepinone derivative, m.p. 258° (Barchet and Merz listed m.p. 264° for their product). Although it has not been possible to obtain the isomeric diazepinone, our experience with pairs of isomeric dihydrodiazepinones would lead us to predict a difference of 20° or more in the melting points of the two compounds. We therefore feel that our sample, m.p. 258°, is the same material as that obtained by Barchet and Merz (9).

Careful examination of the reaction mixture failed to

reveal the presence of either a pyridylaminocinnamic ester (2) or a pyridyl benzoylacetamide (3), either of which possible intermediates might have suggested the structure of the cyclized material. Neither was it possible to prepare 2 or 3 by alternate synthesis for subsequent conversion to a diazepinone of unambiguous structure. The diazepinone-imidazolone conversion was used to determine the structure of the diazepine product by means of the following sequence, which takes advantage of the α-styryl function as a blocking group:

Dry fusion of the dihydrodiazepinone (m.p. 258°) at 250° afforded an N-α-styrylpyridoimidazolone in almost 80% yield after several crystallizations. The imidazolone system was easily recognizable by its characteristic ultra-violet spectrum and by the presence of a typical carbonyl absorption peak at 5.80 μ in the infrared. The α-styryl substituent was indicated by a carbon-carbon olefinic

double bond in the infrared and by the appearance of two vinyl proton signals, *cis* and *trans* to the phenyl ring, at δ 5.67 and 6.07 ppm, respectively, in the nmr. The rearrangement product was alkylated by means of 2-bromopropane in dimethylsulfoxide in the presence of potassium carbonate. Acid hydrolysis of the resulting *N*-α-styryl-*N'*-isopropyl compound removed the acid labile α-styryl moiety of the enamine, leaving an *N*-isopropylpyridoimidazolone, m.p. 159°.

Comparison of this material with an authentic sample of 1,3-dihydro-3-isopropyl-2*H*-imidazo[4,5-*b*]pyridin-2-one (6) showed identity by all criteria evaluated. The authentic sample of 6 was prepared by an unambiguous synthesis involving isopropylamination of 2-chloro-3-nitropyridine, reduction of the resulting 2-isopropylamino-3-nitropyridine (7) to the *ortho*-diamine 8, and cyclization of 8 with phosgene in warm toluene.

The unequivocal establishment of structure 6, formed *via* alkylation and hydrolysis of the thermal rearrangement product, now permits correct characterization of the dihydrodiazepinone. The presence of the isopropyl group in 6 at the imidazolone 3-position requires the presence of the α-styryl function at the 1-position in 5. Thus, the thermal rearrangement product must be structure 4 and, since the carbon-nitrogen bond is not cleaved during the thermal rearrangement, 4 could arise only from the 2-phenyl-4-one diazepine, 1a, and not from the alternate cyclization product 1b. The structure of the diazepinone product from the reaction of 2,3-diaminopyridine and ethyl benzoylacetate was, therefore, correctly assigned by Barchet and Merz despite their failure to consider the alternate cyclization possibility.

EXPERIMENTAL (10)

Ultraviolet absorption spectra were measured with Cary Model 11 and Model 15 spectrophotometers in 95% ethanol solution. Infrared spectra were determined with a Perkin-Elmer Model 137B spectrophotometer. Nmr spectra were obtained by means of a Varian A-60 spectrometer with tetramethylsilane as the internal standard; the solvent was anhydrous deuteropyridine (stored over Linde 4A molecular sieves). Thin layer chromatography was carried out on Eastman Chromagram plates, with 1-butanol saturated with water as the solvent system. Melting points were taken by the capillary method at a rate of heating of 2°/minute in a modified Wagner-Meyer melting point apparatus (11) and are corrected for stem exposure. Drying of analytical samples was carried out at 70° for 17 hours *in vacuo* over phosphorus pentoxide.

3,5-Dihydro-2-phenyl-4*H*-pyrido[2,3-*b*] [1,4]diazepin-4-one (1a).

A mixture of 1.09 g. (0.01 mole) of 2,3-diaminopyridine and 2.88 g. (0.015 mole) of ethyl benzoylacetate in 80 ml. of xylene was brought to a boil, and the water, which was formed during the reaction, was separated by azeotropic distillation. Tan crystals began to form after 1 hour and the mixture was heated for an additional 3 hours to complete the reaction. After being cooled, the product was separated by filtration and was crystallized twice

from xylene to give pale yellow needles, 1.5 g. (65%), m.p. 258° (lit. (5): 264°); uv: λ max 251, 275, and 320 mμ.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.05; H, 4.85; N, 17.56.

1,3-Dihydro-1-α-styryl-2*H*-imidazo[4,5-*b*]pyridin-2-one (4).

Compound 1a (0.45 g., 1.9 mmoles) was placed in a test tube which was plunged into a hot (250°) Woods metal bath. The brown melt was maintained at 250° for 20 minutes. The crude product was crystallized once from xylene and twice from benzene. Two additional crystallizations from ethanol-water gave fluffy white crystals, m.p. 172-174°. The yield was 0.35 g. (78%); uv: λ max 240 and 293 mμ; ir: λ max (potassium chloride) 5.80 (strong carbonyl), 6.12 (C=C), 6.22 (aromatic) μ; nmr: δ 5.67 (1H) and 6.07 (1H) ppm.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N. 17.71. Found: C, 70.82; H, 4.80; N, 17.54.

1,3-Dihydro-1-α-styryl-3-isopropyl-2*H*-imidazo[4,5-*b*]pyridin-2-one (5).

To a solution of 0.59 g. (2.5 mmoles) of 4 in 10 ml. of dimethylsulfoxide were added 0.31 g. (2.5 mmoles) of 2-bromopropane and 0.35 g. (2.5 mmoles) of potassium carbonate. The mixture was warmed at 55-60° for 18 hours. An additional quantity of 2-bromopropane (0.62 g., 5 mmoles) was added and the mixture warmed at 55-60° for another 18 hours in order to ensure complete reaction. The reaction mixture was poured over ice and the gummy solid was triturated under the water until it hardened into an off-white powder. Four crystallizations from ligroin (b.p. 65-90°) gave white crystals, m.p. 95-100°; uv: λ max (ε) 241 (14,100) and 294 (11,100) mμ; ir: λ max (potassium chloride) 5.84 (strong carbonyl), 6.11 (C=C), 6.22 (aromatic), 7.18 (C-CH₃) μ.

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.14; N, 15.05. Found: C, 72.97; H, 6.19; N, 14.89.

1,3-Dihydro-3-isopropyl-2*H*-imidazo[4,5-*b*]pyridin-2-one (6).

A. By Direct Synthesis.

Phosgene was passed at a slow rate for 0.5 hour through 25 ml. of toluene and to this saturated solution was added 0.36 g. (2.4 mmoles) of 2-isopropylamino-3-aminopyridine (8). The pale yellow reaction solution was refluxed gently for 5 hours. After overnight cooling (small quantity of precipitate present), the reaction mixture was reduced to half volume and extracted several times with 10% sodium hydroxide solution (10 ml. total). The combined sodium hydroxide extracts were acidified with dilute hydrochloric acid. The aqueous solution was reduced to two-thirds volume and refrigerated. The resulting white precipitate was separated, dried and crystallized three times from ligroin (b.p. 65-90°) to give fine white needles, m.p. 159.5-160.5°; uv: λ max (ε) 229 (3,450) and 292 (12,310) mμ; ir: λ max (potassium chloride) 2.90, 3.18, 3.33, 5.90, 6.08, 6.16, 6.30, 6.78 (shoulder), 6.90 (doublet), 7.25 (shoulder), 7.30, 8.00, 8.35, 8.82, and 9.00 μ; nmr: δ 3.60 (6H doublet), 4.87 (1H multiplet), and 10.92 (broad 1H), ppm, as well as the 3 pyridine ring protons.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: C, 60.99; H, 6.40; N, 23.50.

B. By Hydrolysis of 5.

A sample of 5 (2.29 g., 8.2 mmoles) was dissolved in 35 ml. of a solution of sulfuric acid, water, and ethanol (1:1:2 by volume) and the reaction mixture was gently warmed for 1 hour. Neutralization of the reaction solution with 10% sodium hydroxide (to pH 8) precipitated white crystals and a brown oil. The mixture was

shaken with chloroform to remove acetophenone and the product (6). The chloroform extract was evaporated and the residue was washed with a small volume of ether to remove the acetophenone. The remaining pale yellow powder was crystallized from ligroin (b.p. 65-90°) to give small white needles, m.p. 156-157°, in 41% yield.

The uv, ir, and nmr spectra and the behavior of this material on thin layer chromotography were identical with those of 6, prepared by procedure A. Mixture melting point determination (m.p. 157-158°) showed no depression.

2-Isopropylamino-3-aminopyridine (8).

To a solution containing 5.55 g. (0.035 mole) of 2-chloro-3-nitropyridine (Aldrich Chemical Company) dissolved in 400 ml. of absolute ethanol was added with stirring at room temperature 4.13 g. (0.07 mole) of isopropylamine. The temperature was raised to 45-50° and stirring was continued at this temperature until the ultraviolet spectrum indicated the reaction to have gone to completion. The reaction solution was concentrated to a volume of 40 ml. This solution containing unpurified 2-isopropylamino-3-nitropyridine (7), (uv: λ max 225, 267, and 413 mμ) was hydrogenated in the presence of 5% palladium-charcoal (200 mg.) on a Parr apparatus. After overnight shaking, the catalyst was separated and the brown reaction solution was evaporated to dryness. The resulting black oil was redissolved in benzene and the solution re-evaporated to azeotropically remove all traces of ethanol. The remaining black tarry solid was dried under vacuum overnight. Repeated crystallizations of the crude material from ligroin (b.p. 65-90°) with the aid of charcoal finally afforded white needles, m.p. 113-116°; uv: λ max 250 and 312 mμ. The yield was 0.95 g. or 18%, based upon the starting 2-chloro-3-nitropyridine. The diamine 8 is sensitive to light and air; the analytical sample was wrapped in foil and sealed under nitrogen.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.66; N, 27.80. Found: C, 63.68; H. 8,70; N, 27.58.

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