

Application of a Thermal Rearrangement Reaction to Questions of Structure of Condensed Dihydrodiazepinones: Characterization of the Isomeric Diazepinone Products from 3,4-Diaminotoluene and Ethyl 4,4,4-Trifluoroacetoacetate (1)

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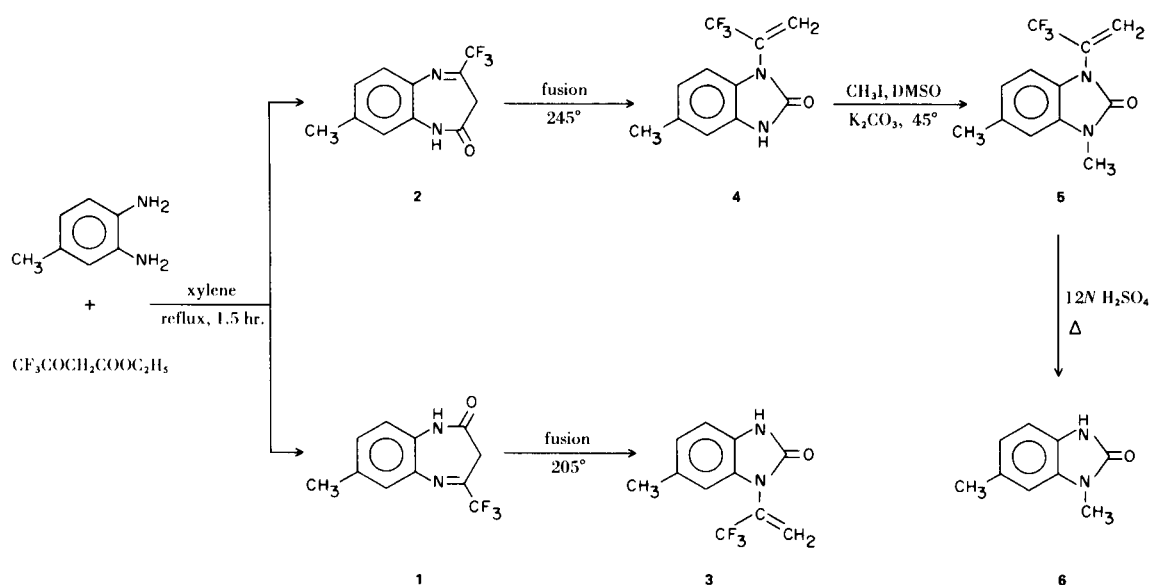
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In connection with studies on the chemistry of diazepine derivatives, we observed that, when heated in the absence of solvent, condensed dihydrodiazepinones are easily rearranged into *N*-alkenylimidazolones (2). The structural relationship between the imidazolone product and the diazepinone from which it is derived provides a convenient method for characterizing diazepinones of ambiguous structure. Such diazepine products result when unsymmetrical diamines are condensed with β -ketoesters. We have previously described the characterization of the diazepinone product from 2,3-diaminopyridine and ethyl benzoylacetate (3) and the isomeric diazepinones from 3,4-diaminopyridine and ethyl acetoacetate (4) by means of this method. We now wish to report on the isomeric diazepinone derivatives from 3,4-diaminotoluene and ethyl 4,4,4-trifluoroacetoacetate. In the present study, the

thermal rearrangement reaction not only aided in the characterization of the alternate ring closure products but it first provided evidence for the presence of those products in the reaction mixture.

Ethyl 4,4,4-trifluoroacetoacetate was condensed with 3,4-diaminotoluene in boiling xylene with azeotropic removal of water and ethanol. Initially, when crystallized from xylene, the reaction product appeared to be a single, pure diazepinone product on the basis of microchemical analysis, thin layer chromatography, and spectral evidence. However, on further examination, it was found that, although the entire sample crystallized from a large volume of carbon tetrachloride, only about two-thirds of the material dissolved in hot carbon tetrachloride at a ratio of 50 ml. of solvent per gram of solid. The material which crystallized from carbon tetrachloride melted at 202-203°;

SCHEME 1



that which failed to dissolve melted at 238-240°. The two samples gave identical nuclear magnetic resonance spectra in deuteriopyridine and identical ultraviolet absorption spectra in ethanol and aqueous pH 1 solution. Although some small differences in the regions of 6.30-6.80 and 8.15-8.60 microns in the infrared were observed, the two samples proved inseparable by thin layer chromatography. On the basis of the available data, it was impossible to tell whether the two samples were the isomeric ring closure products, **1** and **2**, or whether they were merely tautomeric forms of the same diazepinone product.

As noted above, the condensation of an unsymmetrical diamine with a β -ketoester is inherently complicated by the possible formation of isomeric dihydrodiazepinone products. Some reactions, for example, those of 2,3-diaminopyridine and ethyl acetoacetate in boiling xylene (**5**), 3,4-diaminopyridine and ethyl acetoacetate in boiling toluene (**4**), and 2,3-diaminopyridine and ethyl benzoylacetate in boiling xylene (**3**), lead to the formation of one diazepinone product exclusively. Other reactions, for example, that of 4,5-diaminopyrimidine and ethyl acetoacetate in boiling xylene (**6**), afford mixtures of the two theoretically possible diazepinone products. Where pairs of isomeric diazepinones were available for study (**7**), we found for the two compounds different migrational values on thin layer chromatography and clear differences in their spectral properties. However, as an added complication, we have also observed in several instances (**4**, **5**, **6**, **8**) the ability of condensed dihydrodiazepinones to exist in two stable tautomeric forms in the solid state. In such tautomeric pairs, the two species exhibit unique infrared spectra when sampled as potassium chloride disks. Although they may even have different melting points, they give identical nuclear magnetic resonance and ultraviolet absorption spectra and are inseparable by thin layer chromatography.

Based upon previous experience, it appeared that the two samples from the reaction of 3,4-diaminotoluene and ethyl 4,4,4-trifluoroacetoacetate were tautomers of the same diazepinone product. However, when the diazepinone sample, m.p. 202-203°, was heated at just above its melting temperature, there was formed a benzimidazolone derivative, m.p. 138-141°. Fusion of the diazepinone sample, m.p. 238-240°, at 245° afforded a benzimidazolone, m.p. 203-206°. Mixture melting point determination of the two imidazolone samples gave a melting range of over 30°, and, although they did not effectively separate on thin layer chromatography, their nmr spectra in the aromatic region and their infrared spectra were different. Clearly, the imidazolone products were isomeric and, therefore, must have been derived from isomeric diazepinones.

Scheme 1 shows the isomeric dihydrodiazepinones, **1** and **2**, the isomeric benzimidazolones, **3** and **4**, and the

sequence by which the imidazolone melting at 203-206° was characterized as 5-methyl-1-trifluoroisopropenylbenzimidazolone, **4**. Methylation of the imidazolone, m.p. 203-206°, with methyl iodide in dimethylsulfoxide in the presence of potassium carbonate afforded an *N*-trifluoroisopropenyl-*N'*-methyl derivative. The trifluoromethyl group rendered the alkenyl moiety resistant to acid hydrolysis, but the enamine was eventually cleaved by the action of hot 12 *N* sulfuric acid. The resulting dimethylbenzimidazolone was identified as the 1,6-dimethyl compound, **6**, by comparison with an authentic sample prepared by catalytic reduction of 3-methylamino-4-nitrotoluene, followed by cyclization of the unpurified diamine with phosgene in warm benzene. Ricci and Vivarelli (9) have reported the synthesis of **6** *via* fusion of 3-methylamino-4-aminotoluene dihydrochloride with urea. The melting point of our authentic sample of **6** agreed with the value reported by the Italian workers.

The relative positions of the two methyl substituents in **6** served as the basis for assigning structures to all products involved in this investigation. The location of the methyl group in **6** on the nitrogen atom *meta* to the aromatic methyl substituent requires the presence of the trifluoroisopropenyl function at the other imidazolone nitrogen atom in **5**. The imidazolone with melting point 203-206°, which was methylated to give **5**, must therefore be 5-methyl-1-trifluoroisopropenylbenzimidazolone, **4**. Since no carbon-nitrogen bonds are cleaved during the rearrangement of dihydrodiazepinones into *N*-alkenylimidazolones (**2**), the diazepinone material, m.p. 238-240°, from which **4** was derived, is structure **2**. The diazepinone melting at 202-203° is therefore **1** and its rearrangement product, m.p. 138-141°, is **3**.

Interruption of the reaction of 3,4-diaminotoluene and ethyl 4,4,4-trifluoroacetoacetate in refluxing xylene at various times in an attempt to isolate a possible intermediate was unrewarding. The formation of alternate ring closure products in approximately a 2:1 relationship in this reaction suggests a possible electronic influence due to the methyl substituent on the aromatic diamine. However, the mechanism by which these products are formed remains unclear.

EXPERIMENTAL (10)

Ultraviolet absorption spectra were measured with Cary Model 11 and Model 15 spectrophotometers in 95% ethanol, except where pH 1 (0.1 *N* hydrochloric acid) is indicated as solvent. Infrared spectra were determined as potassium chloride disks with a Perkin Elmer Model 137B double beam spectrophotometer. Nmr spectra were obtained by means of a Varian A-60 spectrometer with tetramethylsilane as the internal standard. 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.

Condensation of 3,4-Diaminotoluene with Ethyl 4,4,4-Trifluoroacetoacetate.

A mixture of 7.32 g. (0.06 mole) of 3,4-diaminotoluene and 16.56 g. (0.09 mole) of ethyl 4,4,4-trifluoroacetoacetate in 400 ml. of xylene was heated at reflux for 1.5 hours, the water and ethanol formed during the reaction were separated continuously by azeotropic distillation (Dean-Stark trap). Upon cooling, the solution deposited a gray crystalline solid, which was collected, washed with cyclohexane, and air-dried (13.2 g., 91%). The crude product was treated with hot carbon tetrachloride (50 ml./g.) and the portion of material which failed to dissolve was separated and saved. The carbon tetrachloride solution, upon cooling, gave a quantity of off-white needles. The material which failed to dissolve was treated a second time with hot carbon tetrachloride and, again, the insoluble portion was collected; the cooled carbon tetrachloride solution gave additional off-white needles, which were combined with the first crop. Two crystallizations of this material, once with charcoal, from a minimal volume of carbon tetrachloride gave 8.13 g. (56%) of 2,3-dihydro-7-methyl-4-trifluoromethyl-1*H*-1,5-benzodiazepin-2-one (**1**), m.p. 202-203°; ir: λ max 2.90, 3.07, 3.18, 3.35 (sh), 5.93, 6.01, 6.20, 6.37, 6.61 (sh), 6.69, 6.75 (sh), 7.01, 7.26, 7.45, 7.83, 8.20 (sh), 8.30, 8.48, 8.80, 8.99, and 9.46 μ .

Anal. Calcd. for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.74; F, 23.53; N, 11.57. Found: C, 54.66; H, 3.72; F, 23.51; N, 11.46.

The white powder which had not dissolved at a ratio of 50 ml. of hot carbon tetrachloride per g. of compound was crystallized from a large volume of carbon tetrachloride. Crystallization gave 3.83 g. (25%) of 2,3-dihydro-8-methyl-4-trifluoromethyl-1*H*-1,5-benzodiazepin-2-one (**2**), m.p. 238-240°; ir: λ max 2.90, 3.07, 3.18, 3.40, 5.93, 6.01, 6.20, 6.38, 6.61, 6.78, 7.01, 7.26, 7.43, 7.83, 8.18, 8.33, 8.49, 8.57, 8.81, 8.99, and 9.46 μ .

Anal. Found: C, 54.34; H, 3.70; F, 23.30; N, 11.45.

The two isomers exhibited identical ultraviolet absorption and nuclear magnetic resonance spectra and were inseparable by thin layer chromatography; uv: λ max 225 and 303 nm; λ max (pH 1) 216, 248 (sh), and 287 nm; nmr (deuteriopyridine): δ 2.28 (3H, singlet), 3.65 (2H, singlet), and 7.00-7.53 (3H, multiple peaks, aromatic) ppm.

6-Methyl-1-trifluoroisopropenylbenzimidazolone (**3**).

A test tube containing 3.0 g. (0.012 mole) of **1** was plunged into a hot (205°) oil bath; the white sublimate which formed above the heated area was repeatedly scraped back into the melt. After 40-45 minutes, when sublimation had ceased, the tube was removed from the oil bath and permitted to cool. The dark brown solid was loosened from the walls of the tube by trituration under ethanol (2 ml.). Ligroin was added and the tan powder which was present was collected. Several crystallizations from ligroin (b.p. 65-90°) gave small white crystals of **3** (1.9 g., 63%), m.p. 138-141°; uv: λ max 226 (sh) and 285 nm; ir: λ max 3.16, 3.27, 3.50, 5.84, 6.00 (sh), 6.13, 6.20, 6.68, 6.80, 7.17, 7.58, and 7.78 μ ; nmr (deuteriochloroform): δ 2.38 (3H, singlet), 6.05 (1H, multiplet, $J = 6$ Hz), 6.50 (1H, multiplet, $J = 6$ Hz), and 6.78-7.23 (3H, multiple peaks, aromatic) ppm.

Anal. Calcd. for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.74; F, 23.53; N, 11.57. Found: C, 54.38; H, 3.69; F, 23.24; N, 11.59.

5-Methyl-1-trifluoroisopropenylbenzimidazolone (**4**).

A 3.23 g. sample (0.013 mole) of **2** was rearranged to **4** according to the procedure described for **3**, except that a temperature of 240-245° was used. Crystallization of the product from cyclohexane gave 2.7 g. (84%) of **4** as small white crystals, m.p.

203-206°; uv: λ max 226 (sh) and 285 nm; ir: λ max 3.13 (sh), 3.20, 3.29, 3.47, 3.59, 5.84, 6.00, 6.13, 6.20, 6.65, 6.80, 7.10, 7.18, 7.42, 7.58, and 7.78 μ ; nmr (deuteriochloroform): δ 2.38 (3H, singlet), 6.05 (1H, multiplet, $J = 6$ Hz), 6.50 (1H, multiplet, $J = 6$ Hz), 6.92 (2H, fine splitting, aromatic), and 7.02 (1H, fine splitting, aromatic) ppm.

Anal. Calcd. for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.74; F, 23.53; N, 11.57. Found: C, 54.54; H, 3.64; F, 23.27; N, 11.67.

1,6-Dimethyl-3-trifluoroisopropenylbenzimidazolone (**5**).

To a suspension of 450 mg. (1.9 mmoles) of **4** in 4 ml. of dimethylsulfoxide was added 240 mg. (1.9 mmoles) of potassium carbonate and 1.06 g. (four-fold excess) of methyl iodide. The mixture was stirred at 45° overnight, then poured over ice. The resulting brown gum was hardened to a yellow powder by trituration under cold water. Several crystallizations of the material from ligroin (b.p. 65-90°) gave white crystals (330 mg., 69%), m.p. 105-106°; uv: λ max 227 (sh), 285, and 290 (sh) nm; ir: λ max 3.21, 3.33, 3.40, 5.84, 6.05, 6.19, 6.25, 6.69, 6.80, 7.02, 7.20, 7.28 (sh), 7.49, 7.71, and 7.81 μ ; nmr (deuteriochloroform): δ 2.43 (3H, singlet, C-CH₃), 3.43 (3H, singlet, N-CH₃), 5.97 (1H, multiplet, $J = 6$ Hz), 6.45 (1H, multiplet, $J = 6$ Hz), 6.87 (1H, multiplet, $J = 3$ Hz), and 6.93 (2H, singlet) ppm.

Anal. Calcd. for $C_{12}H_{11}F_3N_2O$: C, 56.25; H, 4.33; F, 22.25; N, 10.94. Found: C, 56.55; H, 4.20; F, 22.03; N, 11.15.

Hydrolysis of **5**.

A suspension of 1.5 g. (6 mmoles) of **5** in 5 ml. of 12*N* sulfuric acid was heated gradually with stirring to 135°. The mixture was kept at 135° until a clear yellow solution was obtained (ca. 10 minutes). The temperature was then lowered to 90°, a few drops of water were added, and the reaction was stirred at 90° for 4 hours. The mixture was poured over ice and the resulting aqueous solution was adjusted to pH 7 by addition of dilute ammonium hydroxide. Trituration of the resulting oil under ice water gave a white solid. Crystallization several times from ligroin (b.p. 65-90°) gave 820 mg. (87%) of 1,6-dimethylbenzimidazolone (**6**) as long white needles, m.p. 214-216° [lit. (9): 210-212°]; uv: λ max (ϵ) 231 (6300) and 287 (7500) nm; ir: λ max 3.17, 3.30, 3.42, 3.51, 5.95, 6.25, 6.71, 6.80, 6.88, 6.94, 7.21, 7.74, and 7.90 μ ; nmr (deuteriochloroform): δ 2.42 (3H, singlet, C-CH₃), 3.42 (3H, singlet, N-CH₃), and 6.80-7.00 (3H, aromatic, multiple peaks) ppm.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.64; H, 6.21; N, 17.28. Found: C, 66.87; H, 6.22; N, 17.19.

An authentic specimen of 1,6-dimethylbenzimidazolone (**6**) was prepared for comparison by hydrogenation of 3-methylamino-4-nitrotoluene in ethanol in the presence of 5% palladium on charcoal, followed by treatment of the unpurified diamine with phosgene in warm (60°) benzene. The spectral properties, not heretofore described, of the product, m.p. 214-215°, were identical with those of the material obtained from the hydrolysis of **5**; mixture melting point determination showed no depression.

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