SYNTHESIS OF A NOVEL HETEROCYCLIC SYSTEM, INDOLO[2',3':5,6][1,2,4]TRIAZINO[2,3-a] BENZIMIDAZOLE

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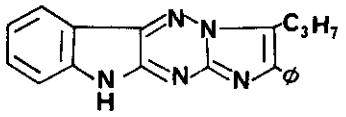
Abstract - The incorporation of both the benzimidazole and triazinoindole moieties in a new ring system has been accomplished via the condensation of 1, 2-diaminobenzimidazoles with various isatins. The alkylation of one of the products (4a) was investigated.

Our previous interest in benzimidazoles,[1] triazinoindoles,[2] and their reported antiviral properties, prompted us to incorporate both rings into a new heterocyclic system. Since Russian investigators[3] had previously reported the condensation of 1,2-diamino-4-phenyl-5-n-propylimidazole with isatin to afford 1,[3]



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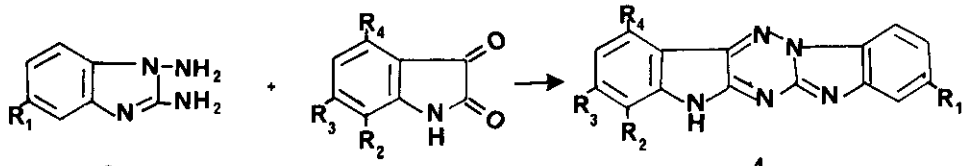
we attempted the condensation of 1,2-diaminobenzimidazole[1] (2) with isatin (3). The product of this reaction was found to be the pentacyclic compound, 7H-indolo[2',3':5,6][1,2,4]triazino[2,3-a] benzimidazole (4). The general nature of the reaction was tested by condensing 1,2-diaminobenzimidazole (2) and 1,2-diamino-5-chlorobenzimidazole[1] (2c) with substituted isatins (3a-c)[4a-c] to afford the corresponding pentacyclic derivatives (4a-c).



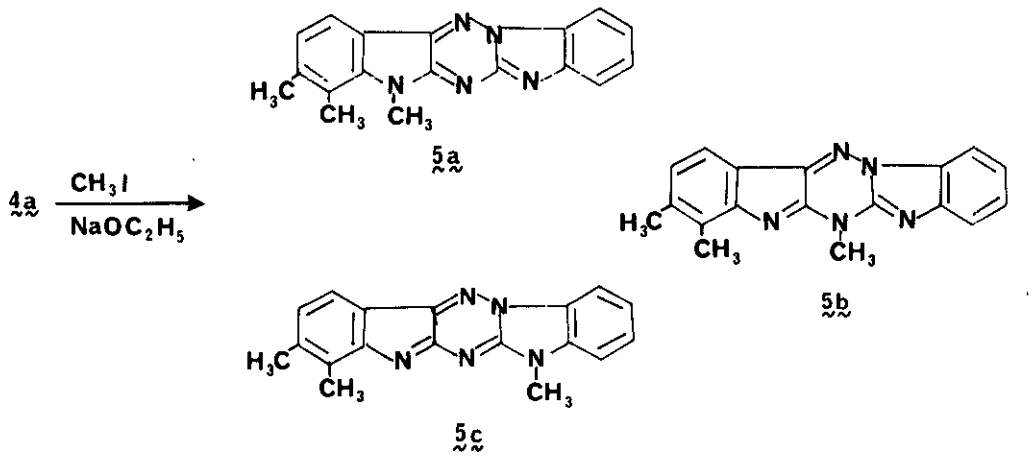
2 + 3 → 4

a: R_1 = H; R_2, R_3 = CH_3; R_4 = H

b: R_1 = H; R_2 = CF_3; R_3, R_4 = H

c: R_1 = Cl; R_2 = OCH_3; R_3 = H, R_4 = Cl

The alkylation of this new ring system was thought of interest, as several sites were available for N-alkylation. Compound 4a was chosen for this study since its aromatic methyl groups could facilitate NMR characterization of the alkylation products. Alkylation of 4a, accomplished with methyl iodide and sodium methoxide, resulted in the formation of three products (5a-c) which were separated by column chromatography.



The structure of 5a was assigned unequivocally by comparing its chemical and physical properties with those of the product obtained from the condensation of 2 with 1,6,7-trimethylisatin. The structures of 5b and 5c were assigned on the basis of their NMR spectra which showed resonances for N-methyl groups at δ 3.75 and δ 4.38 respectively, in agreement with their environment.

EXPERIMENTAL SECTION[5]

Melting points were determined on a Mel-Temp melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were recorded on a Beckman Model DB double beam spectrophotometer. NMR spectra were taken on a Varian A-60A spectrometer. Elemental analyses were carried out by Robertson Laboratory, Florham Park, New Jersey.

General Procedure for the Preparation of Indolo[2',3':5,6][1,2,4]triazino[2,3-a]benzimidazoles (4, 4a-c, 5a). The procedure will be illustrated with the preparation of 4. Solutions of 1,2-diaminobenzimidazole (0.0067 mol) and isatin (0.0068 mol) in 50 ml of anhydrous ethanol were mixed and refluxed in the presence of a catalytic amount of potassium hydroxide (1N) for 4.5 hours. The product (4) was isolated by filtration, (95% yield), mp > 430°d; NMR(CF_3CO_2H): δ 7.00-7.49 and 7.72-8.12 (m,broad, 8H); IR(KBr): 3000, 1605 and 1515 cm^{-1}; UV(C_2H_5OH), λ_{max} (log ε): 232 (4.06), 272 (4.39), 282 (4.45), 291 (4.45), and 365 (3.93) nm.

Compound 4a required a reflux period of 8 hours, (74% yield), mp 445° d; NMR (CF_3CO_2H): δ 2.08 (s, 6H), 7.02 (d,1H, J = 7.8), 7.72 (d, 1H, J = 7.8), 7.25-7.53 (m, 3H), and 7.87-8.10 (m, 1H); IR(KBr): 3020, 1610 and 1515 cm^{-1}; UV(C_2H_5OH), λ_{max} (log ε): 235 (4.04), 274 (4.27), 282 (4.44), 292 (4.50), and 370 (3.94) nm.

Compound 4b required a reflux period of 8 hours (80% yield), mp 370-371°d; NMR (CF_3CO_2H): δ 7.08-7.53 (m, 4H), 7.80 (d, 1H, J = 8.4), 7.96-8.20 (m, 1H), and 8.33 (d, 1H, J = 8.4); IR(KBr): 3000, 1605, and 1510 cm^{-1}; UV(C_2H_5OH), λ_{max} (log ε): 234 (4.11), 278 (4.38), 292 (4.37), 302 (4.37), and 368 (3.96) nm.

Compound 4c required a reflux period of 30 hours (45% yield), mp > 445° d; NMR (CF_3CO_2H): δ 3.63 (s, 3H), 6.87-6.97 (m, 2H), 7.39 (s, broad, 2H), and 7.80-7.95 (m, 1H); IR(KBr): 3050, 1620, and 1505 cm^{-1}; UV(C_2H_5OH), λ_{max} (log ε): 272 (3.80), 287 (3.81), 297 (3.88), and 365 (3.29) nm.

Compound 5a was prepared from 2 and 1, 6, 7-trimethylisatin as described for 4 (96% yield), mp 332-333°; NMR (CF_3CO_2H): δ 2.22 (s, 3H), 2.48 (s, 3H), 4.03 (s, 3H), 7.15 (d, 1H, J = 8.4), 7.85 (d, 1H, J = 8.4) and 7.42-8.17 (m, 4H); IR(KBr): 1595 and 1515 cm^{-1}; UV(C_2H_5OH), λ_{max} (log ε): 234 (3.93), 275 (4.19), 284 (4.38), 294 (4.46), and 372 (3.82) nm. All compounds (4a-c, 5a) are bright orange or reddish-orange solids.

Methylation of 4a. A solution of sodium ethoxide, freshly prepared from sodium (1.6g, 0.0024 ga) and 75 ml of absolute ethanol, and methyl iodide (2 ml, 0.0322 mol) were added to a solution of 4a (0.6996g, 0.0024 mol) in 50 ml of absolute ethanol. The reaction mixture was heated for 2.5 hours at which point it was still incomplete (tlc). More methyl iodide (2 ml) was added and the mixture was refluxed 16.5 hours longer. After standing at ambient temperature for 48 hours, the red solid that formed was removed by filtration and the solvent evaporated to afford additional solid. The combined solids were extracted with absolute ethanol at 5°. A dark red purple solid remained. This solid was reslurried with 15 ml of ethanol to afford 0.0102g of a pure compound later identified as 5,8,9-trimethylindolo[2',3':5,6][1,2,4]triazino[2,3-a]benzimidazole (5c). Tlc analysis (silica gel, chloroform/ethanol 20:1 v/v) of the combined filtrates indicated the presence of three major components at R_f 0.96, 0.83, and 0.70. The filtrate was concentrated to 3 ml and its components separated by column chromatography (silica gel, 60 cm x 17 mm). The initial eluting solvent was chloroform/ethanol (20:1 v/v). The polarity of the solvent was then increased to chloroform/ethanol (6:1 v/v) for the final fractions.

Evaporation of the solvent from fraction (R_f 0.96) afforded 0.1120g of a red purple solid whose chemical and physical properties were identical to those of the alcohol insoluble solid isolated in the earlier extraction procedure. The combined yield of 5c was 0.1222g (17%) mp > 350° d; NMR (CF_3CO_2H): δ 2.15 (s, 6H), 4.38 (s, 3H), 7.29 (d, 1H, J = 7.8) , 7.94 (d, 1H, J = 7.8),

7.42-8.22 (m, 4H); IR(KBr): 1625 and 1550 cm^{-1}; UV(C_2H_5OH), λ_{max} (log ε): 234 (3.65), 270 (4.09), 280 (4.12), 288 (4.19), and 376 (3.67) nm.

Evaporation of the solvent from the second fraction (R_f 0.83) gave an orange crystalline product which proved to be identical to 5a prepared by an unequivocal method. The yield of 5a was 0.3583g, 49.6%, mp > 445°d. The third fraction (R_f 0.70) contained 0.1815g (25% yield) of an orange crystalline solid, mp > 340°d, which was identified from its spectral properties as 6,8,9-trimethylindolo[2',3':5,6][1,2,4]triazino[2,3-a]benzimidazole (5b); NMR (CF_3CO_2H): δ 2.07 (s, 6H), 3.75 (s, 3H), 7.05 (d, 1H, J = 7.8), 7.79 (d, 1H, J = 7.8) and 7.33-8.13 (m, 4H): IR(KBr): 1605 and 1515 cm^{-1}; UV (C_2H_5OH), λ_{max} (log ε): 234 (4.07), 272 (4.17), 282 (4.41), 292 (4.46)and 367 (3.88) nm.

REFERENCES AND NOTES

1. A. V. Zeiger and M. M. Joullie, Synthetic Comm. 1976, 6, 457; J. Org. Chem., 1977, 42, 542.
2. W. A. Romanchick, Ph.D. Dissertation, University of Pennsylvania, 1978; W. A. Romanchick and M. M. Joullie, Heterocycles, 1978, 9, 1931.
3. V. M. Dziomko and A. V. Ivashchenko, Khim. Geterotsikl. Soedin., 1973, 9, 1190.
4. a) H. Columbara, United States Patent 1856210 (1932); Chem. Abstracts , 1932, 26, 3523.
   b) Purchased from ROC/RIC Chemical Corp., 507 Main St., Belleville, N.J. 07109.
   c) P. M. Maginnity and C. A. Gaulin, J. Amer. Chem. Soc., 1951, 73, 3579.
5. Elemental analyses were obtained for all compounds and were in good agreement with theoretical values (0.3%).

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