Imino-Bridged Heterocycles. VII. [1] *N*-Aminobenzocycloheptapyridinimines

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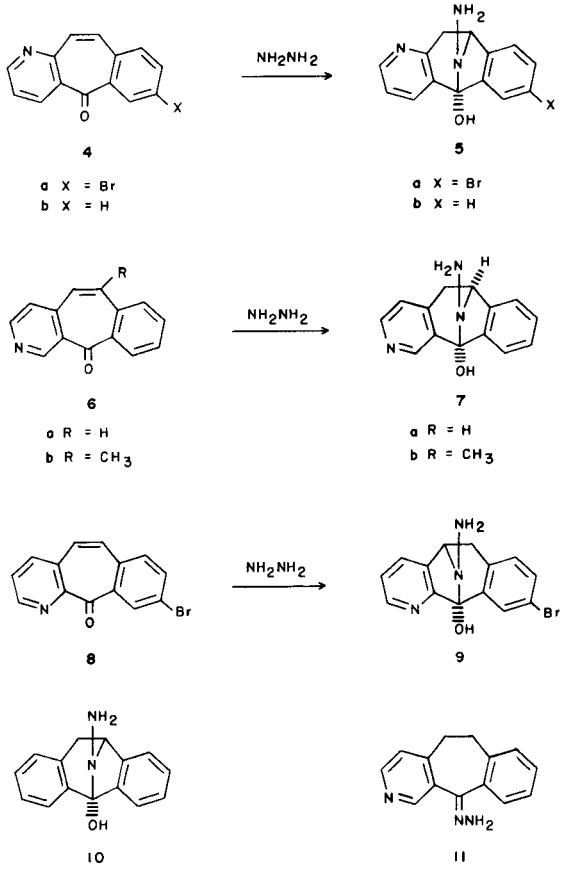
Received February 10, 1986

Condensation of anhydrous hydrazine with a variety of benzocycloheptapyridinones led to *N*-aminobenzocycloheptapyridinimines. Regiospecific ring closures occurred in all the systems investigated.

J. Heterocyclic Chem., **23**, 1331 (1986).

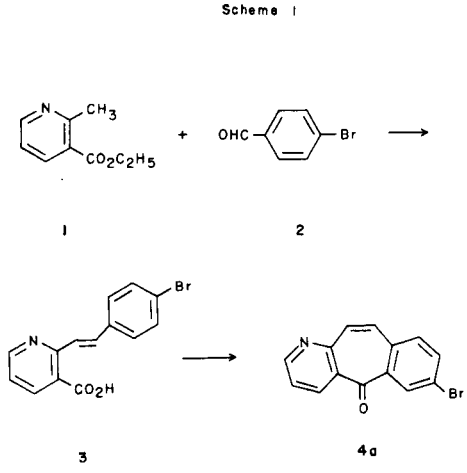
From our recent interest in bridged benzocycloheptapyridines [1] and the report that 5-*H*-dibenzo[*a,d*]cyclohepten-5-one reacts with hydrazine to form **10** [3], we were prompted to investigate the reaction of hydrazine with related benzocycloheptapyridinones. All of the products formed resulted from the addition of hydrazine to the carbonyl without loss of water, followed by regiospecific cyclizations of the secondary amino function into the olefinic bridge. The ketones used have been reported with the exception of **4a** which was prepared according to Scheme 1.

Treatment of the four ketones, **4a, 4b, 6a** and **6b**, with hot anhydrous hydrazine generated the stable, crystalline



4 5 6 7 8 9 10 11

Scheme I



1 2 3 4a

N-aminobenzocycloheptapyridinimines, **5a, 5b, 7a** and **7b**. Support for these structural assignments is provided by the fact that none of the products displayed carbonyl absorption in the infra-red, and they clearly were adducts of hydrazine with the starting materials and not dehydration products as indicated by the analytical data. The regiochemical assignments were based on analogy with other imino-bridged structures resulting from regiospecific cyclization [4a,b] and spectroscopic studies.

The proton nmr data showed the loss of the olefinic protons with characteristic patterns depicting a bridged species [4a,b]. In direct analogy with Hardtmann [3], the chemical shift of H-10 in **5a** (4.48) and H-6 in **7a** (4.55) was more consistent with an amino bridge than an oxygen bridge, precluding that isomeric structure. The lack of spin-spin splitting in the 6-CH_3 function of **7b** confirmed that this was the position of attachment for the imino bridge in this product. NOE experiments on bridgehead protons confirmed the other assignments.

While these products arose through regiospecific cyclizations through a conjugated 2- or 4-vinylpyridine derivative, we wondered whether a system not conjugated directly with the pyridine nitrogen, as in **8** [5], similar to a 3-vi-

nyl pyridine, would show any regio preference. The product isolated from reaction of **8** with hydrazine did come from a regiospecific addition, however the bridging amino added to the olefinic linkage next to the pyridine at C-5 to give **9**. The regiochemistry was conclusively established through an NOE experiment. Positive NOE's were observed for H-3 and H-5 and a small negative NOE was observed for H-2 upon irradiation of H-4. Similarly, irradiation of H-6α produced positive NOE's in H-5, H-6β, H-7 and H-4. A negative NOE was also observed for H-8. The negative NOE's are due to multiple transfers of polarization, a phenomenon known as "the three spin effect" or as "indirect polarization" [6]. Corresponding NOE's in the H-6 protons were not observed upon irradiation of H-7, presumably due to offsetting effects of direct and indirect polarization transfer.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected values. The ^{1}H nmr spectra were recorded on a Varian T-60 or GE NT-360 spectrometer using TMS as an internal standard. Microanalyses were performed under the direction of Dr. William C. Randall by Ms. Jan Stranick.

2-[*trans*-2-(4-Bromophenyl)vinyl]pyridine-3-carboxylic Acid (**5**).

A mixture of sodium hydride (2.0 g, 53% oil dispersion, 0.045 mole), alcohol (4.5 g, 0.06 mole) and DMF (55 ml) was warmed until hydrogen evolution ceased, *ca.* 0.5 hour. The resulting mixture was cooled to 0-5°, **1** [4a] (5.0 g, 0.03 mole) in 5 ml of DMF was added, and 0.75 hour later 4-bromobenzaldehyde (6.73 g, 0.036 mole) in 5 ml of DMF was introduced. The resulting mixture was stirred overnight as the temperature rose to 25°. The reaction mixture was diluted with 200 ml of cold water and acidified with acetic acid. The solid that separated was filtered and dried, 8.73 g, mp 207-217°. Recrystallization from methanol gave material with mp 213-233°.

Anal. Calcd. for $C_{14}H_{10}BrNO_2$: C, 55.28; H, 3.31; N, 4.61. Found: C, 55.48; H, 3.33; N, 4.48.

7-Bromobenzo[4,5]cyclohepta[1,2-*b*]pyridin-5-one (**4a**).

The acid **3** (5 g) was added to hot PPA (100 g) at 220° and the resulting mixture was stirred for 0.75 hour at 220-225°, then cooled to 100°. The mixture was poured into water (600 ml) and made alkaline by the addition of 20% sodium hydroxide solution. Extraction of the basic solution with methylene chloride gave 3.12 g of crude brown solid, that was recrystallized from ethyl acetate to give 1.6 g beige solid, mp 137-138.5°.

Anal. Calcd. for $C_{14}H_8BrNO$: C, 58.76; H, 2.82; N, 4.90. Found: C, 58.57; H, 2.58; N, 4.99.

12-Amino-7-bromo-10,11-dihydro-5-hydroxybenzo[4,5]cyclohepta-[1,2-*b*]pyridin-5,10-imine (**5a**).

A mixture of **4a** (0.50 g) and anhydrous hydrazine (3 ml) was heated at reflux for 3 hours. Excess hydrazine was removed under vacuum and the residue was recrystallized from acetonitrile, 0.20 g, mp 216-218°; ^{1}H nmr (DMSO-d_6): δ 2.53 (d, J = 18 Hz, H-11α, 1H), 3.50 (dd, J = 18, 6 Hz, H-11β, 1H), 4.48 (d, J = 6 Hz, H-10, 1H), 7.0-7.53 (m, H-3, H-6, H-8, H-9, 4H), 7.87 (dd, J = 8, 2 Hz, H-4, 1H), 8.33 (dd, J = 6, 2 Hz, H-2, 1H).

Anal. Calcd. for $C_{14}H_{12}BrN_3O$: C, 52.84; H, 3.80; N, 13.21. Found: C, 53.05; H, 3.64; N, 13.38.

12-Amino-10,11-dihydro-5-hydroxybenzo[4,5]cyclohepta[1,2-*b*]pyridin-5,10-imine (**5b**).

A mixture of **4b** [7,8] (0.50 g) and anhydrous hydrazine (3 ml) was heated under reflux for 0.75 hour. Excess hydrazine was removed under vacuum and the residue was treated with hot acetonitrile to give 0.36 g of white solid, mp 190-199°. Additional recrystallization from acetonitrile raised the mp to 199-202°.

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 69.99; H, 5.51; N, 17.59.

12-Amino-5,6-dihydro-11-hydroxybenzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine (**7a**).

A mixture of **6a** [4a] (20 g) and anhydrous hydrazine (100 ml) was heated under reflux for 18 hours. Excess hydrazine was removed under vacuum and the residue was dissolved in hot acetonitrile (700 ml). The solution was treated with Darco, filtered and concentrated to 400 ml. A brown solid was collected, 4.6 g, mp 177-179°. Subsequent recrystallization from acetonitrile gave material with mp 182.5-183°; ^{1}H-nmr (deuteriochloroform): δ 2.55 (d, J = 18 Hz, H-5α, 1H), 3.32 (dd, J = 18, 6 Hz, H-5β, 1H), 4.55 (d, J = 6 Hz, H-6, 1H), 6.84 (d, J = 5 Hz, H-4, 1H), 7.23 (br s, H-7, H-8, H-9, H-10, 4H), 8.31 (d, J = 5 Hz, H-3, 1H), 8.72 (s, H-1, 1H).

From the first mother liquor above there was obtained 2.1 g of orange crystals, p 141-143°. Recrystallization from acetonitrile gave mp 149-151°, identified as 5,6-dihydrobenzo[5,6]cyclohepta[1,2-*c*]pyridin-5-one hydrazone, **11**; ^{1}H nmr (deuteriochloroform): δ 3.02 (s, -CH_2CH_2-, 4H), 4.05 (br s, NH_2, 2H), 6.83 (d, J = 5 Hz, H-3, 1H), 7.05 (s, H-7, H-8, H-9, H-10, 4H), 8.23 (d, J = 5 Hz, H-3, 1H), 8.73 (s, H-1, 1H).

12-Amino-5,6-dihydro-11-hydroxy-6-methylbenzo[5,6]cyclohepta-[1,2-*c*]pyridin-6,11-imine (**7b**).

A mixture of **6b** [4b] (2.0 g) and anhydrous hydrazine (12 ml) was heated to reflux for 0.5 hour. Excess hydrazine was removed under vacuum and the residue was treated with hot acetonitrile (150 ml) to give 1.71 g of white crystals, mp 225-227°; ^{1}H nmr (deuteriochloroform): δ 1.76 (s, 6-CH_3, 3H), 2.44 (d, J = 19 Hz, H-5α, 1H), 2.50 (br s, NH_2, 2H), 3.09 (d, J = 19 Hz, H-5β, 1H), 6.83 (d, J = 5 Hz, H-4, 1H), 7.13-7.33 (m, H-7, H-8, H-9, H-10, 4H), 8.39 (d, J = 5 Hz, H-3, 1H), 8.86 (s, H-1, 1H).

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.97; N, 16.59. Found: C, 71.02; H, 6.07; N, 16.66.

12-Amino-9-bromo-5,6-dihydro-11-hydroxybenzo[5,6]cyclohepta[1,2-*b*]-pyridin-5,11-imine (**9**).

A mixture of **8** [5] (2.0 g) and anhydrous hydrazine (12 ml) was heated under reflux for 1 hour. Excess hydrazine was evaporated under vacuum and the residue was crystallized from acetonitrile, 0.55 g, mp 194-196°; ^{1}H nmr (DMSO-d_6): δ 2.41 (d, J = 17.9 Hz, H-6α, 1H), 3.36 (dd, J = 17.9, 4.9 Hz, H-6β, 1H), 4.43 (d, J = 4.9 Hz, H-5, 1H), 6.99 (d, J = 8.2 Hz, H-7, 1H), 7.21 (dd, J = 7.5, 5.0 Hz, H-3, 1H), 7.37 (dd, J = 8.1, 2.2 Hz, H-8, 1H), 7.69 (d, J = 2.2 Hz, H-10, 1H), 7.77 (dd, J = 7.5, 1.2 Hz, H-4, 1H), 8.26 (dd, J = 5.0, 1.2 Hz, H-2, 1H).

Anal. Calcd. for $C_{14}H_{12}BrN_3O$: C, 52.84; H, 3.80; N, 13.21. Found: C, 52.90; H, 3.80; N, 13.37.

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