

Derivatives of 10,11-Dihydro-5H-dibenzo[*a,d*]cycloheptene and Related Compounds VII. (1). Improved Syntheses of 11-*H*-Benzo[5,6]cyclohepta[1,2-*c*]pyridin-11-one

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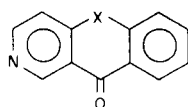
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An improved synthesis of the title compound is described. The base catalyzed condensation of 4-methylnicotinonitrile with benzaldehyde resulted in the isolation of *trans*-4-styrylnicotinamide (**2a**) in high yield. Hydrolysis to the acid and heating the acid **3a** with polyphosphoric acid (ppa) gave the title compound **1a** in good yields. Even higher yields of **1a** were obtained in the presence of catalytic quantities of selenium. Also described are two other syntheses of the title compound as well as the preparation of a series of compounds related to **2a** (Table I).

To prepare large quantities of certain aminoalkyl derivatives of 11-*H*-benzo[5,6]cyclohepta[1,2-*c*]pyridin-11-one (**1a**) it was necessary to develop improved syntheses of this compound. The original (2) preparation of **1a** involved the selenium dioxide dehydrogenation of **1b**, a method which was not readily adaptable to large scale preparation. This report describes our work in this

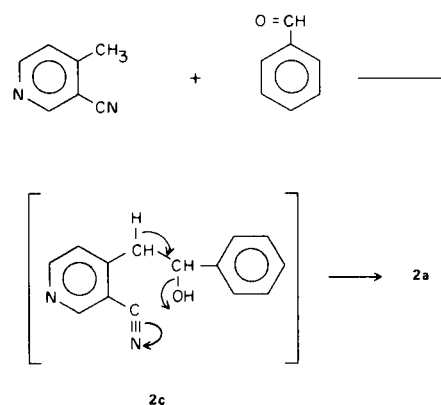


1a X = CH₂-CH₂
1b X = CH₂-CH₃

area and is summarized in Chart 1.

The readily available, 4-methylnicotinonitrile (**3**) was condensed with benzaldehyde in the presence of potassium *t*-butoxide in *t*-butyl alcohol and benzene (Method A) or sodium methoxide in methanol (Method B) to give the *trans* nicotinamide **2a** in high yield. The formation of **2a** is probably the result of an internal dehydration-hydration reaction, *in situ*, of the intermediate hydroxynitrile **2c** as shown.

Support for the proposed intramolecular transfer of water is given by the similar reaction of methyl-4-methylnicotinate and benzaldehyde which produced the *trans* acid **3a** directly at -40° in short reaction times. These reaction conditions, as well as careful isolation procedures, practically exclude the possibility of a two step dehydration and saponification during the reaction and subsequent workup.

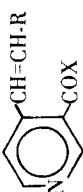


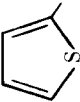
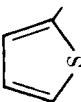
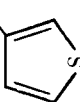
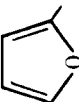
The base-catalyzed condensation of 4-methylnicotinonitrile with a series of hetero-arylaldehydes was also carried out. The *trans* nicotinamide derivatives as well as the acids obtained therefrom by hydrolysis (method C) are listed in Table I.

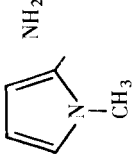
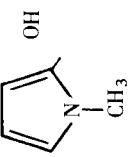
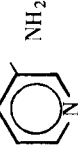
Compounds **2a** and **3a** were converted by exposure to diffuse daylight into the *cis* compounds **2b** and **3b** respectively. The structural assignments were based on the infrared spectra. The *trans* compounds showed the characteristic strong absorption in the 10.2-10.6 μ region, which was absent in the spectra of the *cis* compounds (4).

Preliminary attempts at ring closure of either the *trans* (**2a**) or *cis* amides (**2b**) with polyphosphoric acid failed to give the ketone **1a**. Instead, the cyclic lactam **4** was formed as the sole product (5). Compound **4** was recovered unchanged after prolonged heating with ppa at 220-240°.

In contrast, acid **3a** was readily converted to ketone **1a**

TABLE I
Compounds of Formula 

R	X	Method	Yield	M.p. °C	Formula	Calculated		Found		Ir μ	(t)C=C		
						C	H	N	C				
<i>trans</i> C ₆ H ₅	NH ₂	A	80	195-197 (a)									
		B	91	195-197						6.09	10.41 (b)		
<i>cis</i> C ₆ H ₅	NH ₂	D	34	119.5-121	C ₁₄ H ₁₂ N ₂ O	74.96	5.39	12.49	74.83	5.49	12.50	5.95-6.12 (c)	
		C	45	187-189 (e)	C ₁₄ H ₁₁ NO ₂	74.64	4.92	6.22	74.32	4.92	6.26	6.11	10.22 (f)
<i>cis</i> C ₆ H ₅	OH	D	46	180-182 (g)	C ₁₄ H ₁₁ NO ₂	74.64	4.92	6.22	74.47	4.83	6.29	5.80	(h)
		A	35	201-202 (i)	C ₁₂ H ₁₀ N ₂ OS	62.60	4.38	12.17	62.84	4.57	12.25	6.08	10.31
	NH ₂	A	35	201-202 (i)	C ₁₂ H ₁₀ N ₂ OS	62.60	4.38	12.17	62.84	4.57	12.25	6.08	10.31
		B	86										
	OH	C	52	198-200 (e)	C ₁₂ H ₉ NO ₂ S	62.34	3.92	6.06	62.14	3.79	5.99	5.95	10.49
		A	62	207-209 (i)	C ₁₂ H ₁₀ N ₂ OS	62.60	4.38	12.17	62.26	4.41	12.29	6.05	10.25
	OH	C	58	197-200 (i)	C ₁₂ H ₉ NO ₂ S (j)	62.34	3.92	6.06	61.41	3.99	6.16	5.95	10.28
		A	85	184-185 (k)	C ₁₂ H ₁₀ N ₂ O ₂	67.28	4.71	13.08	67.57	4.87	13.10	6.05-6.15 (c)	10.45
	OH	C	86	209-210 (e)	C ₁₂ H ₉ NO ₃	66.96	4.22	6.51	66.66	4.24	6.50	5.95	10.55

	A	66	189-190 (l)	C ₁₃ H ₁₃ N ₃ O	68.70	5.77	18.49	68.35	5.82	18.75	5.97	10.45
	C	50	210-211 (1)	C ₁₃ H ₁₃ N ₂ O ₂	68.41	5.30	12.27	68.48	5.35	12.18	6.05	10.55
	A	32	223-224 (m)	C ₁₃ H ₁₁ N ₃ O	69.32	4.92	18.66	68.96	4.89	18.59	5.95	10.39

(a) M.p. reported 196-197° (Ref. 5). (b) λ max, 228 nm, ϵ 13,798, and λ max, 312 nm, ϵ 27,594. (c) Broad absorption. (d) λ max, 226 nm, ϵ 2,960 and λ max, 283 nm, ϵ 7,855. (e) From ethanol. (f) λ max, 226 nm, ϵ 12,985 and λ max, 313 nm, ϵ 24,470. (g) From methylene chloride-hexane. (h) λ max, 220 nm, ϵ 2,570; λ max, 275 nm, ϵ 6,690 and λ max, 306 nm, ϵ 8,172. (i) From ethylacetate. (j) Hydrochloride salt, m.p. 255-256° from ethanol. Calcd. for C₁₂H₉NO₂S·HCl: C, 53.84; H, 3.77; N, 5.23. Found: C, 52.53; H, 3.85; N, 5.09. (k) From methanol. (l) From benzene. (m) From methanol. (n) From acetonitrile.

in good yield (70-71%) by heating with ppa at elevated temperatures. The differences in reactivity of the amides **2a** and **2b** and the acid **3a** in these cyclization reactions are explained by the nature of the primary reaction products. As noted, the amides were converted into the stable lactam **4**. However, the corresponding cyclic lactone **6** is readily converted into **1a** as was shown with an authentic sample. The pathway to **1a** via **6** was indicated when acid **3a** was heated at 130-140° in ppa. Slow conversion to **1a** took place and the reaction mixture also contained lactone **6**, as shown by thin layer chromatographic analysis. The formation of the lactone corresponding to **6** from 2,6-dimethyl-4-styryl-nicotinic acid under these reaction conditions has been reported (8).

In the presence of selenium the yield of **1a** from the ppa cyclization of **3a** was increased to over 80%, probably due to the catalytic effect of selenium in promoting the conversion of the *trans* acid to the *cis* acid (6,7), the latter having the proper conformation for facile ring closure as the acid.

An alternative synthesis of **1a** involves the condensation of 4-methylnicotinic acid and benzaldehyde in the presence of sodium amide in liquid ammonia, whereby the hydroxy acid **5** was obtained. Treatment of **5** with ppa under the usual high temperature reaction conditions resulted in a 40% yield of **1a**. At lower temperatures (50°) acid **5** was converted into lactone **6**, which on further heating was converted into **1a**.

A second alternative method employed the base-catalyzed condensation of 4-methylnicotinonitrile with ethyl benzoate to give the keto nitrile **7**. Sodium borohydride reduction gave **8**, which on direct ring closure under the usual conditions produced **1a**.

EXPERIMENTAL

trans-4-Styrylnicotinamide (**2a**).

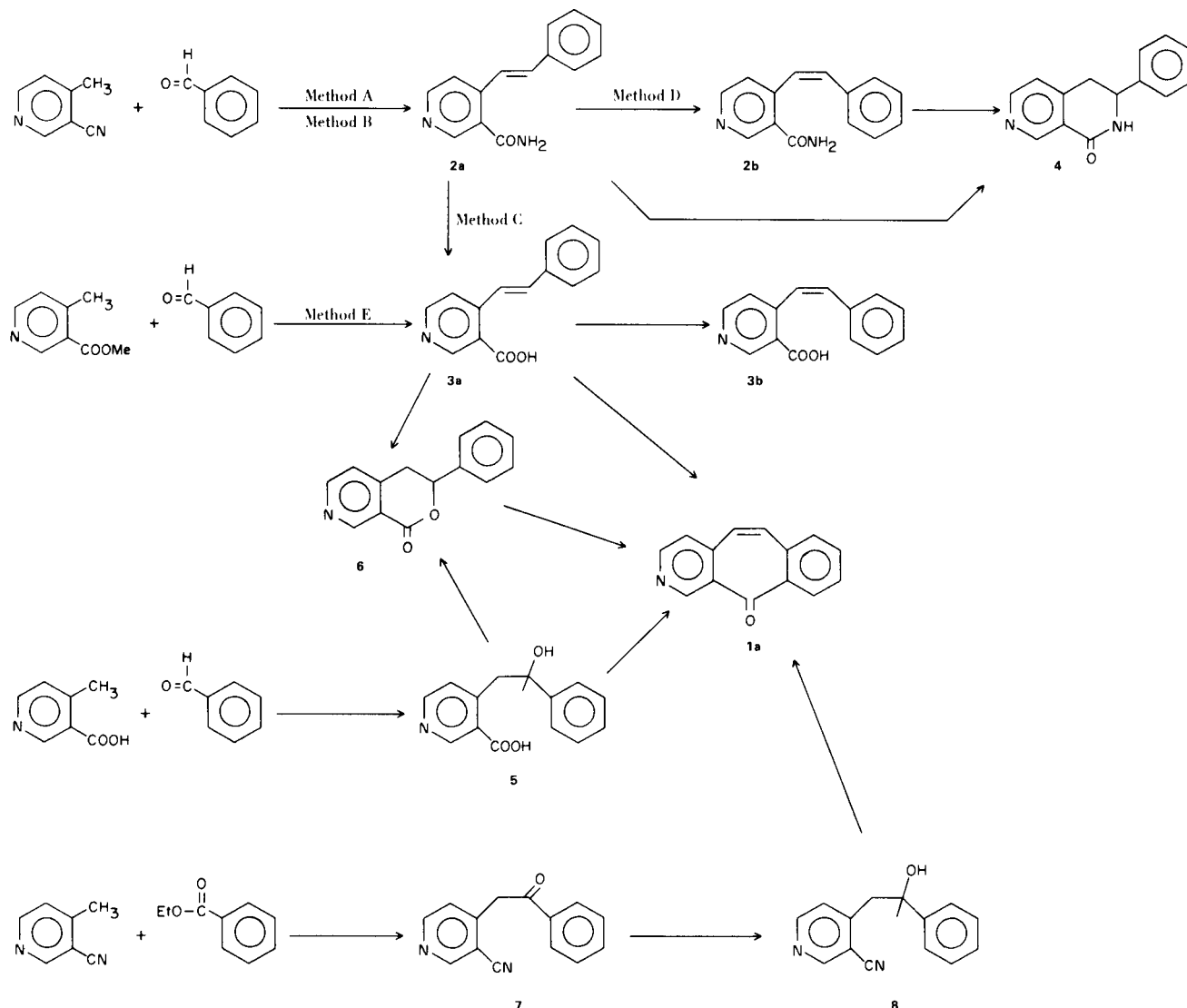
Method A.

To a solution of 112 g. (1 mole) of potassium *t*-butoxide in 1.7 l. of *t*-butyl alcohol under nitrogen, a solution of 118 g. (1 mole) of 3-cyano-4-methylpyridine and 115 g. (1.5 moles) of benzaldehyde in 1.7 l. of benzene was added, and the mixture was heated under reflux with stirring for 10 hours. The reaction was cooled, poured into water, steam distilled, and the residue allowed to crystallize. The product was filtered, air dried and recrystallized.

Method B.

A solution of 29.8 g. (0.55 mole) of sodium methoxide in methanol (500 ml.) was added dropwise at ambient temperature to a stirred solution of 59 g. (0.5 mole) of 3-cyano-4-methylpyridine and 63.5 g. (0.6 mole) of benzaldehyde in methanol (250 ml.) and the mixture was stirred for 18 hours. A solution of ammonium chloride (37 g.) in 1.5 l. of water was added and the mixture was stirred for an additional hour. The product was

CHART I



filtered, washed thoroughly with cold water, air dried and recrystallized.

Alternatively, the methanol solution was poured into water, steam distilled to remove the excess aldehyde and methanol and the residue processed as in Method A.

Saponification to *trans* Acid (3a).

Method C.

In a typical experiment, 30 g. of amide was heated under reflux for 24 hours with 30 g. of potassium hydroxide and 300 ml. of ethanol and 300 ml. of water. The solvents were removed and the residue was dissolved in the minimum amount of water and acidified with acetic acid. The precipitated acid was filtered and recrystallized.

cis-4-Styrylnicotinamide (2b).

Method D.

A solution of 1 g. of 2a in 35 ml. of DMF was exposed to diffuse daylight for 14 days. Water (70 ml.) was added and the

resultant mixture extracted 3 times with methylene chloride. The methylene chloride was evaporated and an equal volume of water was added to the residue precipitating the unchanged *trans* amide, which was filtered off. The filtrate was extracted 3 times with methylene chloride (10 ml. each extract). The combined extracts were dried and the solvent was removed. The residue was triturated with a mixture of methylene chloride-hexane (1:1) and was recrystallized.

trans-4-Styrylnicotinic Acid (3a).

Method E.

A solution of potassium *t*-butoxide (3.36 g., 0.03 mole) in DMF (20 ml.) was added dropwise at -40° to a mixture of methyl 4-methylnicotinate (10) (2.26 g., 0.015 mole) and benzaldehyde (1.59 g., 0.015 mole) in DMF (10 ml.). The mixture was stirred at -40° for 10 minutes and poured into a mixture of ice (50 g.) and ammonium chloride (2.7 g.). The mixture was acidified (pH 4.5) with 20% hydrochloric acid and the solution was cooled to $0-5^{\circ}$ for 2 hours to complete the

crystallization. The product was filtered, washed with cold water and air dried; yield 2.96 g. (87.7%) m.p. 189-191°, which did not depress the m.p. of a sample prepared by Method C.

4-(2'-Phenyl-2'-hydroxyethyl) Nicotinic Acid (5).

Sodamide was prepared in the usual manner using 9.2 g. (0.4 g.-atom) of sodium in 600 ml. of anhydrous liquid ammonia in the presence of a ferric nitrate catalyst. 4-Methyl nicotinic acid (27.4 g., 0.2 mole) was added cautiously and the mixture was stirred for 1 hour. Benzaldehyde (23.2 g., 0.2 mole) was added dropwise and the mixture stirred for an additional hour. Solid ammonium chloride (20 g.) was added portionwise followed by 250 ml. of anhydrous ether and the ammonia was allowed to evaporate overnight. Water (250 ml.) was cautiously added and layers separated. The aqueous layer, after washing with ether, was acidified with acetic acid and the product allowed to crystallize. The tan solid (16.2 g., 32.6%) was recrystallized from ethanol, m.p. 147-148°.

Anal. Calcd. for C₁₄H₁₃NO₃: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.02; H, 5.30; N, 5.69.

4-Phenacylnicotinonitrile (7).

A solution of 11.8 g. (0.1 mole) of 3-cyano-4-methylpyridine in 50 ml. of DMF was added dropwise at 0° to a stirred suspension of 11.2 g. of potassium *t*-butoxide in 150 ml. of DMF. After 2 hours 15.0 g. (0.1 mole) of ethyl benzoate was added dropwise and the mixture was stirred for 3 hours at 5-10°. The solution was poured onto ice (500 g.) and acidified (acetic acid). The solid was filtered, air dried and recrystallized from isopropyl ether to give 12.4 g. (51%) of product having a m.p. 120-122°.

Anal. Calcd. for C₁₄H₁₀N₂O: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.37; H, 4.43; N, 12.60.

4-(2'-Phenyl-2'-hydroxyethyl)nicotinonitrile (8).

To a suspension of 4.1 g. (0.02 mole) of ketone 7 in 100 ml. of methanol was added slowly at 0°, 2.2 g. (0.06 mole) of sodium borohydride. The mixture was stirred for 2 hours at room temperature and poured into 100 ml. of water. The solid was filtered and recrystallized from benzene-petroleum ether; yield 2.4 g. (54%), m.p. 96-98°.

Anal. Calcd. for C₁₄H₁₂N₂O: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.72; H, 5.38; N, 12.65.

11-*H*-Benzo[5,6]cyclohepta[1,2-*c*]pyridin-11-one.

Method 1. From Acid 3a - With Selenium.

To polyphosphoric acid (900 g.), in which selenium (0.5 g.) was dispersed, was added in several portions with stirring at 225-230°, 45 g. (0.02 mole) of acid 3a, and the mixture was maintained at this temperature for an additional ten minutes. It was cooled to 100° and poured into ice water, basified (aqueous sodium hydroxide), and extracted with chloroform. The extracts were washed with 2% potassium hydroxide solution and with water and concentrated to a residue. The residue (38 g.) was recrystallized from isopropyl alcohol to yield 33.1 g. (80.1%) of a light yellow crystalline solid having a m.p. of 155-157° which was identical with the product previously obtained (1).

Method 2. From Acid 3a - Without Selenium.

The procedure was repeated using the same conditions as in Method 1 except that selenium was omitted. The yield of product was 29.8 g. (71.9%) m.p. 155-157°.

Method 3.

A mixture of 7.2 g. (0.03 mole) of acid 5 in 350 g. of ppa was heated with stirring at 180-190° for 17 hours and poured

into ice water. The mixture was basified (aqueous sodium hydroxide) and extracted with chloroform. The chloroform extracts were washed with water and concentrated on the steam bath. There was obtained 4.7 g. of a brown solid, m.p. 147-148°, which on recrystallization from isopropyl ether had a m.p. of 155-157°; yield, 2.4 g. (38%).

Using this procedure, nitrile 8 was converted into ketone 1a in 27% yield.

3-Phenyl-1-*H*-3,4-dihydropyrano[3,4-*c*]pyridin-1-one (6).

To ppa (150 g.) at 50° was added in portions 10 g. (0.041 mole) of the acid 5 and the mixture was stirred for 10 minutes and poured into water. The solution was basified and extracted with methylene chloride. The extracts were washed with water, and concentrated to a small volume. The product was precipitated by the addition of hexane and recrystallized from methylene chloride-hexane to give 6.0 g. (65%) of 6 having a m.p. of 94-96°.

Anal. Calcd. for C₁₄H₁₁NO₂: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.21; H, 4.92; N, 6.06.

Conversion of 3a to 6 and 1a.

One gram of acid 3a in 15 g. of ppa was heated at 130-140°. The reaction mixture was sampled at 30 minute intervals. The analysis on silica gel (80 parts benzene, 19 parts methanol, and 1 part acetic acid) showed the presence of starting material, ketone 1a, and lactone 6. As the reaction proceeded 3a and 6 disappeared and 1a was formed.

Conversion of 6 to 1a.

The lactone 6 (2 g., 0.009 mole) in 25 g. of ppa was heated to 220-225° for 20 minutes and processed as described. There was obtained 1.12 g. (61.5%) of product having a m.p. of 155-157°, identical in all respects with the ketone 1a, previously prepared.

3-Phenyl-1,2,3,4-tetrahydro-2,7-naphthyridin-1-one (4).

This compound was obtained from the *trans* amide 2a by the method of Bobbitt and Doolittle (5), m.p. 159-161° reported m.p. 160-162°. The same compound was obtained from the *cis* amide 2b by the same method in almost quantitative yield.

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