Derivatives of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and Related Compounds. III. Azaketones (1,2).

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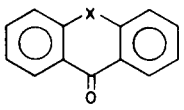
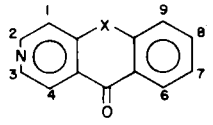
The preparation and properties of four isomeric azadibenzocycloheptenones **3** and their 10,11-dihydro derivatives **2** are described. The ketones **2** were prepared by cyclization of appropriately substituted phenethylpyridine carboxylic acids and dehydrogenated to **3**. Four monochloro derivatives **24** of the 4-azaketone **2d** are also described.

Our investigation (2) of derivatives of 5*H*-dibenzo[*a*,*d*]-cylcoheptene-5-one (**1**) has been extended to include the azaketones represented by formulae **2** and **3** in which one of the aromatic rings of **1** is replaced by a pyridine ring. This report concerns the synthesis and characterization of the isomeric azaketones (3) and some of their chloro substituted derivatives.

The ketones **2** were prepared in good yield by cyclization of the appropriately substituted β-phenethylpyridine carboxylic acid or nitrile using a large excess of polyphosphoric acid. The unsaturated compounds **3** were prepared from the saturated ketones **2** by oxidation with selenium dioxide in pyridine or by bromination-dehydrobromination using *N*-bromosuccinimide and triethylamine (4).

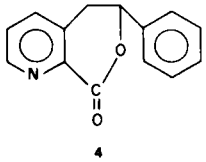


1a, X = CH_2-CH_2
1b, X = CH=CH



2 (X = CH_2-CH_2)
a, 1-aza
b, 2-aza
c, 3-aza
d, 4-aza

3 (X = CH=CH)
a, 1-aza
b, 2-aza
c, 3-aza
d, 4-aza



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Attempts were made to prepare some of the unsaturated ketones **3** by cyclization of the appropriate styrylpyridine acids. In two cases using polyphosphoric acid at moderate temperatures (140°) the lactones **4** and **12** were isolated. At higher temperatures **12** cyclized affording ketone **3a** whereas the very insoluble lactone **4** was recovered unchanged.

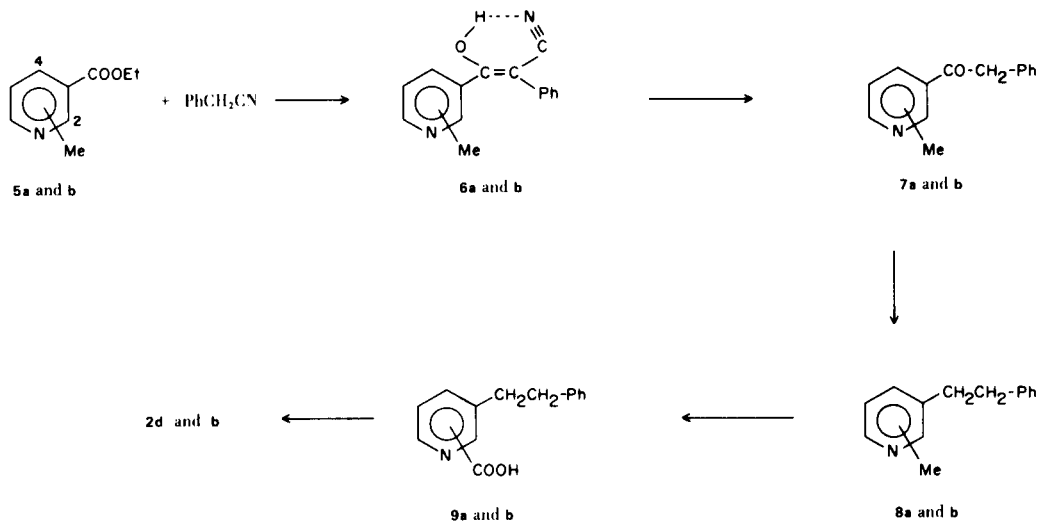
The preparations of the required phenethylpyridine carboxylic acids are presented in the accompanying charts. Condensation of ethyl 2-methylnicotinate **5a** with phenylacetonitrile (Chart I) afforded the nitrile **6a** which was hydrolyzed and decarboxylated to the benzyl pyridyl ketone **7a**. Wolff-Kishner reduction then gave 2-methyl-3-phenethylpyridine (**8a**) which was oxidized to the desired picolinic acid (**9a**) using selenium dioxide in refluxing pyridine. In an exactly analogous series of reactions ethyl 4-methylnicotinate (**5b**) was converted to 3-phenethylisonicotinic acid **9b**. Cyclization of **9a** and **9b** as previously mentioned afforded the 4-aza and 2-azaketones **2d** and **2b**, respectively.

Condensation of ethyl 4-methylnicotinate (**5b**) with benzaldehyde (Chart II) gave the *trans*-stilbazole ester **10** which was saponified and hydrogenated over Raney nickel to 4-phenethylnicotinic acid (**11**). Cyclization then afforded the 3-azaketone **2c**.

In contrast, the condensation of ethyl 2-methylnicotinate (**5a**) with benzaldehyde gave the known (5) lactone **12** (Chart III). Reduction of the latter with phosphorus and iodine in aqueous solution yielded 2-phenethylnicotinic acid (**13**). However, when this reaction was carried out in acetic acid, the major product (69%) was 2-styrylnicotinic acid (**14**) with only a small amount (14%) of **13** being formed. Hydrogenation of **14** afforded the saturated acid **13** which was cyclized to the 1-aza dihydro ketone **2a**. Polyphosphoric acid treatment of **14** at moderate temperature afforded a mixture of the lactone **12** and the unsaturated ketone **3a**. At elevated temperature (180°), however, the lactone was converted directly to **3a** in excellent yield (6).

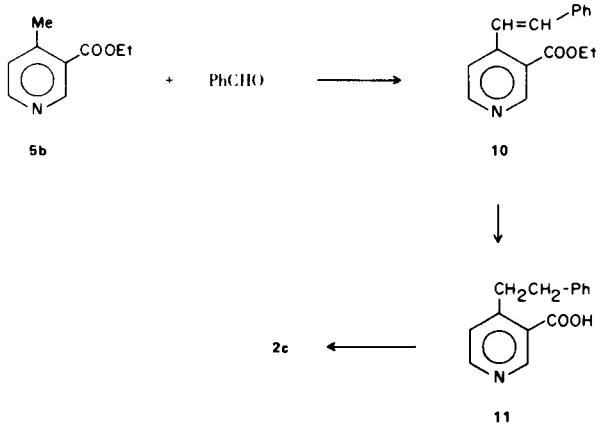
Our interest in the 4-aza compounds was stimulated

CHART I



a series = 2-substituted pyridines
b series = 4-substituted pyridines

CHART II



when certain of their derivatives were shown to have pronounced biological activity (8) and alternate approaches to these compounds and their substituted derivatives were investigated. The methods, summarized in Chart IV, proceeded from *trans*-3-stilbazole (**15**) which was prepared in excellent yield by condensation of 3-pyridinealdehyde and diethyl benzylphosphonate (9). Hydrogenation then afforded 3-phenethylpyridine (**16**) (10) which was converted to the *N*-oxide **17**. Quaternization with dimethyl sulfate followed by addition of potassium cyanide (11) gave a mixture of products from which the 2-cyano compound **18** was isolated as the major product. Careful fractionation of the residue gave the 6-cyano derivative **19a** and the corresponding amide **19b**. The structures of these products were clearly shown by their nmr spectra and by the hydrolysis of **18** to the picolinic acid **9a** or direct cyclization using polyphosphoric acid to the azaketone **2d**. Rearrangement of the *N*-oxide **17** using acetic anhydride gave, after hydrolysis, the pyridones **20** and **21**. Treatment of **20** with phosphorus oxybromide gave the expected 2-bromo compound **22**, whose structure was shown by its nmr spectrum, as well as an unexpected dehydro derivative **23** (12). Metalation of **22** with butyllithium at -50° followed by carbonation gave the acid **9a** in good yield.

CHART III

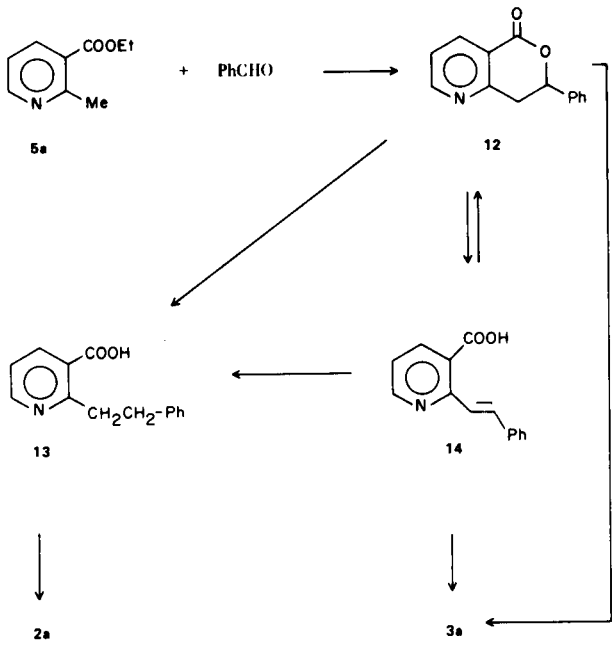
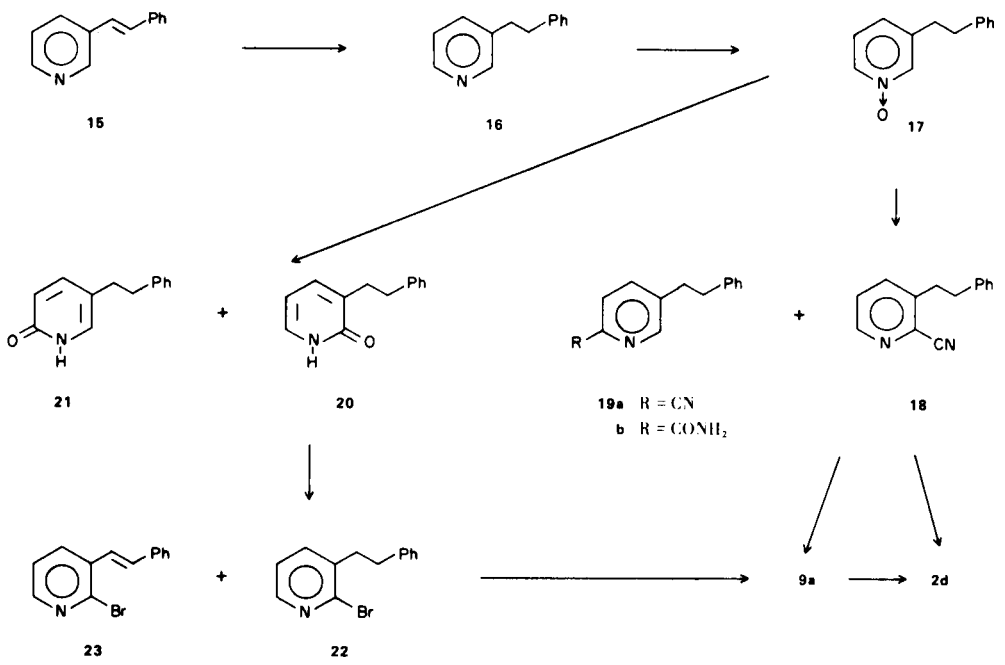


CHART IV



24a R_1 = Cl, R_2 = R_3 = R_4 = H
b R_2 = Cl, R_1 = R_3 = R_4 = H
c R_3 = Cl, R_1 = R_2 = R_4 = H
d R_4 = Cl, R_1 = R_2 = R_3 = H

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Four chloro derivatives **24** of the azaketone **2d** were prepared by polyphosphoric acid cyclization of the corresponding 2-cyanochlorophenethylpyridines (13). The *m*-chlorophenyl compound **25** gave a mixture of ketones **24b** and **24d** which was separated by crystallization. Structural assignments were possible on the basis of the nmr spectra of the two isomers since the hydrogen at position 6 in **24b** was deshielded by the carbonyl group. The carbonyl infrared stretching frequency of ketone **24d** was 30 cm^{-1} higher than the isomeric ketone, consistent with the effect of an *ortho* substituent. In contrast to this latter cyclization in which the need for isomer separation precluded a high overall yield of either product, it was found that hydrolysis of the starting material **25** to the corresponding acid followed by conversion to the acid chloride and cyclization with aluminum chloride gave exclusively the 8-chloroketone **24b** in high yield. This presumably reflects the greater steric demands of the intermediate complex in this type of cyclization.

An attempt to directly chlorinate the unsubstituted 4-azaketone **2d** using one mole of chlorine and silver sulfate in sulfuric acid (14) gave an intractable mixture from which the 7- and 9-chloroketones **24a** and **24c** were isolated in low yields.

The nmr spectra of the aza-dibenzocycloheptenones are given in Tables II and IV and support the structures assigned. The position and coupling constants of the pyridine protons are consistent throughout the series and fall in the expected range (15).

TABLE I

10,11-Dihydroaza-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ones

1. Unsubstituted Azaketones **2** ($C_{14}H_{11}NO$) (a)

Formula No.	Yield %	Recrystallization Solvent	M.P. °C	Analyses, Found C	H	N	Cl
2a	77	hexane	60-62	80.46	5.14	6.61	
2b	63 (b,c)	hexane	46-47	80.40	5.69	7.02	
2c	91 (b)	isopropyl ether	66-68	80.07	5.47	6.65	
2c	80	ethyl acetate	81-82 (d)	80.45	5.32	6.36	

2. Chlorosubstituted Ketones **24** ($C_{14}H_{10}ClNO$) (e)

24a	10 (f)	isopropyl ether	119-121	69.22	4.24	5.88	14.51
24b	34 (g,h)	$CHCl_3$-hexane	105-107	69.18	4.36	5.76	14.68
24c	62 (b)	benzene-hexane	130-132	68.97	4.32	5.79	14.56
24d	9 (g)	$CHCl_3$-hexane	190-191.5	69.00	4.17	5.68	14.78

(a) Calcd: C, 80.36; H, 5.30; N, 6.69. (b) Crude reaction product chromatographed over alumina. (c) Alternatively the crude product was distilled, b.p. 160-165° (0.6 mm), prior to crystallization. (d) On one occasion a second crystalline form m.p. 61-63° was obtained. (e) Calcd: C, 69.00; H, 4.14; N, 5.75; Cl, 14.55. (f) Prepared from crude starting nitrile. (g) Isomers separated by hand picking crystals. (h) Prepared in excellent yield by Friedel-Crafts reaction of the acid chloride (see experimental section).

TABLE II

Spectral Properties of 10,11-Dihydroaza-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ones

Formula No.	IR	UV		NMR, δ (ppm) (a)					
	μ	mμ	ε	H_1	H_2	H_3	H_4	H_6	Other protons
2a	6.07	276	(10,150)		q 8.67 (4.5, 2)		q 8.43 (8.25, 2)	m 7.99	CH_2-CH_2, m 3.36
2b	6.09	271	(9,950)	m 8.33 (includes H_3)				m 7.65	CH_2-CH_2, s 3.12
2c	6.09	268	(11,800)		d 8.53 (5)		s 9.14	m 7.94	CH_2-CH_2, s 3.14
2d	5.98	280	(10,200)	q 7.56 (7.5, 1.75)		q 8.60 (4.5, 1.75)		m 8.00	CH_2-CH_2, s 3.08
24a	5.93	278	(8,500)	q 7.87 (7.5, 1.75)		q 8.61 (4.5, 1.75)			CH_2-CH_2, m 3.24
24b	6.00	282	(13,000)	q 7.75 (8, 1.75)		q 8.78 (4.5, 1.75)		q 8.14 (8, 0.8)	CH_2-CH_2, s 3.21
24c	5.95	280	(8,700)	q 7.65 (7.5, 1.75)		q 8.70 (4.5, 1.75)		d 8.03 (2)	CH_2-CH_2, s 3.18
24d	5.83	284	(7,900)	q 7.33 (7, 2)		q 8.35 (4, 2)			CH_2-CH_2, s 3.06

(a) Obtained by first order analysis only. The letters s, d, q, m denote the multiplicities of the peaks (singlet, doublet, quartet, multiplet). The numbers in brackets are the observed splittings in Hz. In all cases the integrals support the assignments shown.

TABLE III

Aza-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ones

Formula No.	Method	Yield, %	Recrystallization Solvent	M.P. °C	Analyses, Found (a) C	H	N
3a	C	70	hexane	96-97	80.97	4.39	7.14
3b	B	47	hexane	132-133	81.15	4.55	6.67
3c	A	62	hexane	157-158	81.18	4.32	6.73
3d	A	57 (b)	ethyl acetate	116-118	80.99	4.72	

(a) Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. (b) After chromatography over alumina.

TABLE IV

Spectral Properties of Aza-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ones

Formula No.	IR μ	UV mμ	ϵ	NMR, δ (ppm) (a) H_1	H_2	H_3	H_4	H_6	$H_{10,11}$ (b)
3a	6.05	226	(21,600)		q 8.89		q 8.53	m 8.28	7.23, 7.35
		246	(25,000)		(4.5, 1.75)		(8.5, 1.75)		(12)
		305	(11,850)						
		350	(3,400) (c)						
3b	6.05	235	(25,600)	s 8.88		d 8.73	d 8.00	m 8.25	7.04, 7.16
		258	(14,800) (c)			(5)	(5)		(12)
		310	(12,400)						
		359	(3,300)						
3c	6.08	233	(27,000)	d 7.27	d 8.75		s 9.38	m 8.24	6.87, 7.15
		246	(24,400)	(5)	(5)				(12)
		310	(13,700)						
3d	6.01	226	(21,500)	q 7.89		q 8.83		m 8.23	6.91, 7.13
		255	(29,600)	(7.5, 1.75)		(4.5, 1.75)			(12)
		306	(10,300)						
		348	(2,800)						

(a) Obtained by first order analysis only. The letters s, d, q, m denote the multiplicities of the peaks (singlet, doublet, quartet, multiplet). The numbers in brackets are the observed splittings in Hz. In all cases the integrals support the assignments shown. (b) AB quartet. (c) Shoulder.

EXPERIMENTAL (16)

α-Cyano-β-[4-methyl-3-pyridyl]-β-hydroxystyrene (**6b**).

To a stirred refluxing solution of sodium methylate (8.1 g., 0.148 mole) in absolute methanol (50 ml.) was added ethyl 4-methylnicotinate (28.4 g., 0.17 mole) and phenylacetonitrile (13.9 g., 0.12 mole). After heating on the steam bath for 6 hours, ice water was added and the solution extracted several times with ether. The aqueous solution was acidified with acetic acid and the precipitate collected by filtration. The crude material (21 g., 74%) was used in the next step. A small sample was crystallized from dilute ethanol, m.p. 195-197°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12; N, 11.86. Found: C, 76.32; H, 5.31; N, 11.67.

α-Cyano-β-[2-methyl-3-pyridyl]-β-hydroxystryene (**6a**).

From ethyl 2-methylnicotinate and phenylacetonitrile by the above procedure this compound was obtained in 71% crude yield. The analysis sample, crystallized from methylene chloride-isopropyl ether had m.p. 171-172°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12; N, 11.86. Found: C, 76.28; H, 5.14; N, 11.87.

p-Chloro-α-Cyano-β-[3-pyridyl]-β-hydroxystyrene.

To sodium ethoxide [from 53.3% sodium hydride (56.3 g.) and absolute ethanol (21 ml.)] and methyl nicotinate (171.3 g.) in toluene (2.5 l.) at 90° was added a solution of *p*-chlorophenylacetonitrile (189.5 g.) in toluene (300 ml.) during 105 minutes. The temperature was maintained for 2 hours then slowly raised

and ethanol distilled out through a helix filled column. The residue was cooled and the precipitate filtered off and dissolved in water. After one extraction with ether the aqueous phase was acidified with acetic acid and the product collected by filtration, 248 g. (84%), m.p. 205-209°. The analysis sample was obtained as orange needles from acetonitrile, m.p. 209-212°.

Anal. Calcd. for $C_{14}H_9ClN_2O$: N, 10.93. Found: N, 10.94.

o-Chloro-α-cyano-β-[3-pyridyl]-β-hydroxystyrene.

From methyl nicotinate and *o*-chlorophenylacetonitrile by the above procedure the title compound was obtained in 46% yield. The analysis sample crystallized from ethyl acetate, m.p. 165-167°.

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.50; H, 3.54; Cl, 13.83; N, 10.93. Found: C, 65.58; H, 3.59; Cl, 13.76; N, 10.88.

Benzyl 4-Methyl-3-pyridyl Ketone (**7b**).

The crude nitrile (**6b**, 85 g.) was refluxed for 16 hours with 48% hydrobromic acid (800 ml.). After pouring into ice-water the mixture was made alkaline with ammonia and extracted with chloroform. The product was distilled *in vacuo* affording **7b** (45 g., 64%), b.p. 153-156° (0.5 mm.), n_D^{25} 1.5823.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.86; H, 6.08; N, 6.80.

Benzyl 2-Methyl-3-pyridyl Ketone (**7a**).

This compound was prepared in 53% yield from **6a** by the same procedure, recrystallized from hexane, m.p. 61-63°.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.46; H, 6.48; N, 6.70.

p-Chlorobenzyl 3-Pyridyl Ketone.

This material was prepared from the corresponding nitrile by the same procedure in 74% yield. It formed needles from dilute ethanol, m.p. 96-98°.

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05; Cl, 15.30. Found: C, 66.90; H, 4.70; N, 5.86; Cl, 15.30.

o-Chlorobenzyl 3-Pyridyl Ketone.

From the appropriate nitrile by the above procedure the title compound was obtained in 82% yield. A sample crystallized from hexane had m.p. 63-66°.

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05; Cl, 15.30. Found: C, 67.46; H, 4.40; N, 5.88; Cl, 15.10.

m-Chlorobenzyl 3-Pyridyl Ketone.

Condensation of methyl nicotinate and *m*-chlorophenylacetonitrile using the method described for the *o*-chloro compound afforded a 66% yield of crude *m*-chloro-α-cyano-β-[3-pyridyl]-β-hydroxystyrene, m.p. 128°. Treatment with 48% hydrobromic acid, as described, then gave the title compound in 67% yield. A sample recrystallized from chloroform-hexane formed plates, m.p. 68-69°.

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05; Cl, 15.30. Found: C, 67.42; H, 4.50; N, 6.08; Cl, 14.95.

4-Methyl-3-phenethylpyridine (**8b**).

A mixture of the ketone **7b** (44 g.), sodium hydroxide (20 g.), 85% hydrazine hydrate (20 ml.) and diethylene glycol (250 ml.) was heated to 240° with continuous removal of water *via* a Dean-Stark trap. The mixture was maintained at this temperature for 3 hours, cooled and poured into water. The product was extracted with ether and the extracts dried and distilled affording 4-methyl-3-phenethylpyridine (29 g., 76%), b.p. 140-142° (3 mm.), n_D^{26} 1.5717.

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.21; H, 7.67; N, 7.05.

Using exactly the same conditions the following phenethylpyridines were obtained:

2-Methyl-3-phenethylpyridine (**8a**).

This compound was obtained in 69% yield, b.p. 130-132° (2 mm.), n_D^{27} 1.5672.

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.43; H, 7.55; N, 7.01.

o-Chlorophenethylpyridine.

This compound was obtained in 59% yield, b.p. 135-136° (1 mm.), n_D^{26} 1.5805.

Anal. Calcd. for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43; Cl, 16.29. Found: C, 71.81; H, 5.56; N, 6.37; Cl, 16.11.

m-Chlorophenethylpyridine.

This compound was obtained in 72% yield, b.p. 145-147.5° (1.2 mm.), n_D^{25} 1.5806.

Anal. Calcd. for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43; Cl, 16.29. Found: C, 71.82; H, 5.15; N, 6.64; Cl, 16.06.

p-Chlorophenethylpyridine.

This compound was obtained in 75% yield, b.p. 174.5° (5.5 mm.), n_D^{25} 1.5793.

Anal. Calcd. for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43. Found: C, 71.71; H, 5.81; N, 6.63.

3-Phenethylisonicotinic Acid (**9b**).

A mixture of 27.5 g. of **8b**, 175 ml. of pyridine and 40 g. of selenium dioxide was heated with stirring under reflux for 3½ hours. Chloroform (150 ml.) was added and the mixture was filtered through supercell and the solvents removed *in vacuo* on the steam bath. The residue was dissolved in dilute ammonium hydroxide, treated with charcoal, filtered and extracted with ether. The aqueous solution was acidified with acetic acid, and product allowed to crystallize. The acid was collected by filtration and recrystallized from dilute ethanol, yield, 18 g. (59%), m.p. 226-227°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.30; H, 6.05; N, 6.15.

3-Phenethylpicolinic Acid (**9a**).

Method 1.

From **8a** by oxidation with selenium dioxide there was obtained 64% of the acid m.p. 98-102° (from isopropyl ether); ir 6.01 μ.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.92; H, 5.70; N, 6.16.

Recrystallization of a sample from concentrated hydrochloric acid gave the hydrochloride m.p. 204° dec.

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.75; H, 5.35; N, 5.31; Cl, 13.45. Found: C, 63.69; H, 5.15; N, 5.24; Cl, 13.51.

Method 2.

A solution of 2-bromo-3-phenethylpyridine **22** (13.1 g., 0.05 mole) in ether (50 ml.) was added during 4 minutes to a stirred ethereal solution of butyllithium (98 ml., 0.0525 mole) at -50° in a nitrogen atmosphere. After stirring for 2 minutes the solution was poured onto a slurry of solid carbon dioxide and ether. After all carbon dioxide had evaporated, 2*N* hydrochloric acid (300 ml.) was added and the precipitated salt collected by filtration. This hydrochloride (8.3 g.) was identical with the sample prepared by method 1. The aqueous filtrate was extracted three times with ether. Evaporation of the solvent afforded a further 2.3 g. of the free acid m.p. 98-102°.

Ethyl 4-Stryrylnicotinate (**10**).

Ethyl 4-methylnicotinate (55.3 g., 0.335 mole), freshly distilled benzaldehyde (71.0 g., 0.67 mole) and acetic anhydride (60 ml.) were refluxed for 24 hours under nitrogen. The excess anhydride was removed *in vacuo*, the residue poured into water and extracted with ether. The ether solution was extracted with dilute hydrochloric acid and the acid extracts after preliminary washing with ether were basified with ammonia. The product was extracted with chloroform and distilled, yield 35 g. (41%), b.p. 190-196° (2 mm.), n^{26}_D 1.6244.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.97; N, 5.53. Found: C, 75.95; H, 5.73; N, 5.57.

4-Styrylnicotinic Acid.

A mixture of 21.2 g. (0.083 mole) of ester (**10**), 21 g. of potassium hydroxide, 20 ml. of water, and 70 ml. of ethanol was refluxed for 6 hours and the solvents removed *in vacuo*. The residue was dissolved in water, and acidified with acetic acid. The product was filtered and recrystallized from ethanol, yield 12 g. (59%), m.p. 195-196°.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.22; H, 5.04; N, 5.99.

4-Phenethylnicotinic Acid (**11**).

Eleven grams of the above stilbazole acid in 200 ml. of ethanol and 10 ml. of 50% sodium hydroxide solution was hydrogenated in a Parr Hydrogenator at 60 psi. initial hydrogen pressure in the presence of Raney nickel catalyst at room temperature. The mixture was filtered, the solvent removed, the residue dissolved in water, acidified and the product collected by filtration and recrystallized from benzene, yield 9.5 g. (82%) m.p. 152-154°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.98; H, 6.10; N, 6.19.

2-Phenethylnicotinic Acid (**13**).

Method 1.

Red phosphorus (8 g.) was slowly added to a cold, stirred mixture of water (58 ml.) and iodine (68 g.). The mixture was stirred for 30 minutes in an ice bath and then 1 hour at room temperature. The lactone **12** (5) (13.5 g., 0.063 mole) was added and the mixture heated under reflux with stirring for 3 hours. Additional red phosphorus (3.7 g.) was added and the mixture heated for an additional 7 hours. The hot solution was filtered, cooled and the precipitated hydriodic acid salt (m.p. 184-186°) collected and dissolved in water. The solution was neutralized with ammonium hydroxide, the product was collected by filtration, air dried and recrystallized from benzene-petroleum ether, yield 8 g. (56%) m.p. 163-164°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.83; H, 5.93.

Method 2.

A solution of 2-styrylnicotinic acid (11.5 g., 0.05 mole) in water (75 ml.) and ethanol (150 ml.) containing sodium hydroxide solution (5 ml., 50%) was reduced over a Raney nickel catalyst in a Parr hydrogenator at an initial pressure of 40 psi. After 30 minutes hydrogenation was complete and the catalyst was removed by filtration. The filtrate was evaporated, the residue taken up in water and acidified with acetic acid. The precipitated product was dried and recrystallized from benzene-petroleum ether, m.p. 164-165°, undepressed on admixture with a sample prepared by method 1.

2-Styrylnicotinic Acid (**14**).

A mixture of glacial acetic acid (250 ml.), red phosphorus (15 g.) and iodine (5 g.) was stirred for 30 minutes at room temperature. Water (5 ml.) and the lactone **12** (5) [45 g., 0.162 mole] were added and the mixture refluxed with stirring for 22 hours. The hot solution was filtered through a sintered glass funnel and the filtrate diluted with iced water. The precipitated salt was collected by filtration, resuspended in water and basified with ammonium hydroxide. Acidification with acetic acid gave the product which was recrystallized from ethanol, yield 25 g. (69%), m.p. 220-221°; λ max 312 mμ; (ε, 26,300).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92. Found: C, 74.91; H, 4.67.

Concentration of the acetic acid solution afforded 5.0 g. (14%) of the saturated acid **13**.

trans 3-Stilbazole (**15**).

To a vigorously stirred solution of 57 g. (0.25 mole) of diethylbenzylphosphonate, 15 g. of commercial sodium methylate and 60 ml. of dry dimethylformamide was added dropwise at 30-35° a solution of 3-pyridine aldehyde (26.8 g., 0.26 mole) in 125 ml. of dimethylformamide. The clear amber colored solution was stirred for an additional 30 minutes at room temperature and poured into 1 liter of ice water. The precipitated product was collected by filtration and air dried, yield 42 g. (92.7%), m.p. 78-80°. A small sample was recrystallized from cyclohexane m.p. 79-80° (lit. m.p. 72-73° (17a) 77-79° (17b).

3-Phenethylpyridine (**16**).

A solution of **15** (18.1 g., 0.1 mole) in ethyl acetate (200 ml.) was hydrogenated in a Parr shaker over 5% palladium on carbon catalyst (1 g.). The catalyst was removed and the product isolated by distillation, b.p. 136-138° (2 mm.); n^{26}_D 1.5694 (lit. (10) b.p. 126-130° (3 mm.). This material was also prepared by Wolff-Kishner reduction of benzyl 3-pyridyl ketone.

3-Phenethylpyridine 1-Oxide (**17**).

A solution of 3-phenethylpyridine (**16**) (183 g., 1 mole) in acetic acid (300 ml.) was heated at 60° for 20 hours with 30% hydrogen peroxide (160 ml.). After pouring onto ice and basifying with ammonia the product was extracted with chloroform. Concentration of the extract and recrystallization from benzene-petroleum ether gave the *N*-oxide (152.4 g., 77%), m.p. 86-90°; λ max 264 mμ (ε, 14,100).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.21; H, 6.23; N, 6.96.

Using identical procudures the following *N*-oxides were prepared: 3-(*o*-Chlorophenethyl)pyridine-1-oxide, recrystallized from methylene chloride-petroleum ether, m.p. 73-75°; λ max 265 mμ (ε, 12,900).

Anal. Calcd. for $C_{13}H_{12}ClNO$: C, 66.83; H, 5.18; N, 5.99; Cl, 15.16. Found: C, 66.97; H, 5.23; N, 5.88; Cl, 15.10.

3-(*m*-Chlorophenethyl)pyridine 1-Oxide.

This compound formed a hydrate, m.p. 44-46°, from aqueous tetrahydrofuran. Extensive drying gave the anhydrous product as an oil.

Anal. Calcd. for $C_{13}H_{12}ClNO$: C, 66.83; H, 5.18; N, 5.99. Found: C, 66.78; H, 5.30; N, 5.79.

3-(*p*-Chlorophenethyl)pyridine 1-Oxide.

This compound crystallized as colorless plates from chloroform-hexane, m.p. 101-102°; λ max 264 mμ (ε, 13,200).

Anal. Calcd. for $C_{13}H_{12}ClNO$: C, 66.83; H, 5.18; N, 5.99; Cl, 15.10. Found: C, 66.72; H, 5.30; N, 6.03; Cl, 15.06.

Reaction of 3-Phenethylpyridine 1-Oxide with Acetic Anhydride.

The *N*-oxide **17** (172 g.) was heated under reflux for 6 hours

with acetic anhydride (875 ml.). The solution was evaporated *in vacuo* and the residue hydrolyzed by refluxing with concentrated hydrochloric acid for 10 hours. After pouring into water the precipitate was collected by filtration and recrystallized from ethanol affording 3-phenethyl-2-pyridone (**20**) (60.6 g., 36%). One further recrystallization from methanol gave the analysis sample, m.p. 187-188°; λ max 297 mμ (ε, 7,100); ir 2.96, 5.95 μ.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: 78.42; H, 6.72; N, 7.10.

The aqueous liquors were basified with ammonia and the precipitated gummy solid (30 g.) collected and combined with a further 10 g. of the same material obtained from the ethanolic residues. Several recrystallizations from methanol gave pure 5-phenethyl-2-pyridone (**21**), m.p. 115-116°; λ max 229 (ε, 12,700) and 307 mμ (ε, 5,900); ir 5.98 μ.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.99; H, 6.40; N, 7.05.

Reaction of 3-Phenethyl-2-pyridone with Phosphorus Oxybromide.

The pyridone **20** (56 g.) and phosphorus oxybromide (180 g.) were heated at 140° for 16 hours. The cooled mixture was poured onto ice, basified with ammonia and the product extracted with ether. Evaporation of the solvent gave an oil (62 g.) which was distilled through a short column. The fraction b.p. 155-158° (2.5 mm.) partially solidified. Several recrystallizations from benzene-petroleum ether gave 2-bromo-*trans*-3-stilbazole (**23**), m.p. 104-106°; λ max 221 (ε, 16,900), 296 mμ (ε, 24,000); ir 6.12 μ; nmr δ 7.00 (d, J = 16 Hz, 1 vinyl H), 7.18-7.67 (m, 7H, aromatic, vinyl and β-pyridyl H), 7.90 (q, J = 7.5 and 2.0 Hz, γ-pyridyl H), 8.27 ppm (q, J = 4.5 and 2.0 Hz, α-pyridyl H).

Anal. Calcd. for $C_{13}H_{10}BrN$: C, 60.02; H, 3.88; N, 5.39; Br, 30.72. Found: C, 59.68; H, 4.23; N, 5.57; Br, 30.67.

The later fractions from the distillation were combined with the mother liquors from crystallization of **23** and redistilled affording 3-phenethyl-2-bromopyridine (**22**), b.p. 142.5° (2 mm.), n_D^{25} 1.5988; λ max 268 mμ (ε, 4,700), nmr δ 3.04 (s, 4H, CH_2-CH_2), 7.2-7.58 (m, 7H, aromatic protons), 8.30 ppm (q, 1H, α-pyridyl H).

Anal. Calcd. for $C_{13}H_{12}BrN$: C, 59.54; H, 4.61; N, 5.34; Br, 30.48. Found: C, 59.66; H, 4.37; N, 5.25; Br, 30.64.

2-Cyano-3-phenethylpyridine (**18**).

To the *N*-oxide **17** (159 g., 0.8 mole) in a nitrogen atmosphere, dimethyl sulfate (100.4 g.) was slowly added. The mixture was stirred at 80-85° for 3 hours, cooled, diluted with water and added to an aqueous solution (330 ml.) of sodium cyanide (117.8 g.) at 0°. The mixture was stirred at this temperature for 3.5 hours and then at 25° for 16 hours. Several extractions with chloroform followed by evaporation of the solvent gave the crude product which was fractionally distilled through a Vigreux column affording the nitrile **18**, 106 g. (64%), b.p. 183-185° (3 mm.), n_D^{25} 1.5763; nmr δ 2.76-3.33 (m, 4H, CH_2-CH_2), 7.05-7.45 (m, 6H, aromatic and β-pyridyl H), 7.59 (q, J = 7.5 and 1.75 Hz, γ-pyridyl H), 8.53 (q, J = 4 and 1.75 Hz, α-pyridyl H).

On prolonged standing a sample of this material crystallized m.p. 36.5-40°.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.42; H, 6.15; N, 12.95.

Hydrolysis of this material by prolonged refluxing with ethanolic sodium hydroxide gave the acid **9a**.

Later fractions from the distillation, after separation of **18**, crystallized on standing. The fraction b.p. 187-198° (1.1 mm.) was recrystallized from isopropyl ether affording 2-cyano-5-phenethylpyridine **19a**, m.p. 55-58°; ir 4.46 μ; nmr δ 2.97 (s, 4H, CH_2-CH_2), 6.94-7.40 (m, 5H, aromatic H), 7.50 and 7.57 (second order splitting, 2H, β and γ-pyridyl H), 8.45 (t, J = 1.5 Hz, 1H, α-pyridyl proton).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 81.10; H, 5.89; N, 13.46.

A fraction b.p. 198-205° (1.0 mm.) was recrystallized from benzene affording 5-phenethylpicolinamide **19b**, m.p. 192-195°; ir 2.89, 3.07, 5.91, 6.0 μ; nmr δ 2.98 (s, 4H, CH_2-CH_2), 7.26 (s, 5H, aromatic H), 7.54 and 8.03 (broad singlets, 2 amide H), 7.7-8.12 (m, 2H, β and γ-pyridyl H), 8.47 (broad singlet, 1H, α-pyridyl H).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.30; H, 6.25; N, 12.27.

Using the identical method described the following nitriles were prepared:

2-Cyano-3-(*p*-chlorophenethyl)pyridine.

This compound was isolated by distillation from the crude reaction mixture. Recrystallization gave colorless plates from isopropyl ether, m.p. 73-74°; ir 4.47 μ; nmr δ 2.75-3.33 (m, 4H, CH_2-CH_2), 7.0-7.63 (m, 6H, aromatic and β and γ-pyridyl H), 8.58 (q, J = 2 and 4.25 Hz, α-pyridyl H).

Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.29; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.51; H, 4.80; N, 11.37; Cl, 14.72.

The higher boiling material from this reaction afforded a 2-cyano-5-(*p*-chlorophenethyl)pyridine which crystallized as plates from chloroform-isopropyl ether, m.p. 116-118°; ir 4.46 μ; nmr δ 2.75-3.2 (m, 4H, CH_2-CH_2), 6.86-7.38 (m, 4H, aromatic), 7.4-7.7 (m, 2H, β and γ-pyridyl H), 8.49 (t, J = 1.25 Hz, α-pyridyl H).

Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.29; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.01; H, 4.58; N, 11.37; Cl, 14.60.

2-Cyano-3-(*m*-chlorophenethyl)pyridine.

This compound was isolated by distillation. Recrystallization from isopropyl ether gave colorless plates, m.p. 72-74°; ir 4.68 μ

Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.29; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.22; H, 4.92; N, 11.60; Cl, 14.23.

The higher boiling fractions from this reaction afforded 2-cyano-5-(*m*-chlorophenethyl)pyridine, recrystallized from isopropyl ether m.p. 47-49°; ir 4.68 μ; nmr δ 2.97 (s, 4H, CH_2-CH_2), 6.86-7.33 (m, 4H, aromatic H), 7.38-7.75 (m, 2H, β and γ-pyridyl H), 8.55 (t, J = 1.5 Hz, α-pyridyl H).

Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.29; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.23; H, 4.60; N, 11.53; Cl, 14.29.

2-Cyano-3-(*o*-chlorophenethyl)pyridine.

This compound was isolated by distillation; the material crystallized from isopropyl ether, m.p. 84-88°; ir 4.67 μ.

Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.29; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.48; H, 4.65; N, 11.46; Cl, 14.72.

General Method for Ring Closure to Azaketones **2a**.

The phenethylpyridine nitrile or acid was heated with fifty times its weight of polyphosphoric acid at 140-160° for 6 hours. The hot solution was poured onto ice, strongly basified with sodium hydroxide and extracted with ether or chloroform. The extracts were dried (sodium sulfate) and evaporated. The product was obtained by chromatography or direct crystallization. The ketones prepared by this method are shown in Table I. Spectral data for the ketones are shown in Table II.

8-Chloro-10,11-dihydro-4-aza-5*H*-dibenzo[*a,d*]cyclohepten-5-one (**24b**).

m-Chlorophenethylpicolinic acid (**18**) (26.2 g., 0.1 mole), suspended in dry benzene (500 ml.) was treated with thionyl chloride

(20 ml.). When the vigorous reaction subsided, the mixture was heated under reflux for 1.5 hours and the solution evaporated *in vacuo*. To the residue, carbon disulfide (600 ml.) was added followed by anhydrous aluminum chloride (26.1 g.) added in portions. The red brown mixture was stirred for 3 hours at room temperature and then allowed to stand a further 16 hours. The mixture was decomposed by addition of dilute hydrochloric acid and the solution extracted with ether. The aqueous layer was basified with sodium hydroxide and the product extracted with chloroform. Evaporation of the solvent afforded crude **24b** which was recrystallized from isopropyl ether, m.p. 100-101°, yield 19.2 g. (77%).

Preparation of Azaketones **3**.

Method A.

The 10,11-dihydroketone (**2**) (16.7 g., 0.08 mole), selenium dioxide (15 g.) and pyridine (60 ml.) were heated under reflux for 4 hours. After cooling the mixture was filtered through Super Cell and the residue washed thoroughly with warm ethanol. The combined filtrate and washings were evaporated *in vacuo* and residue dissolved in dilute hydrochloric acid. After filtration the solution was basified with ammonia and the product collected by filtration and recrystallized. The products are shown in Table III; their spectra appear in Table IV.

Method B.

A mixture of the 10,11-dihydroketone (**2**) (20 g., 0.095 mole), *N*-bromosuccinimide (17.2 g.), benzoyl peroxide (0.2 g.) and carbon tetrachloride (200 ml.) were heated under reflux with stirring for 2 hours. The mixture was filtered and the solvent removed *in vacuo*. To the dark brown residue was added triethylamine (1100 ml.) and the mixture refluxed for 16 hours. The excess solvent was evaporated, the residue dissolved in water and extracted with ether. The ethereal solution was extracted with dilute hydrochloric acid and the acidic extract basified with ammonium hydroxide. The precipitated ketone was collected by filtration, air dried and recrystallized. The products are shown in Table III.

Method C.

The lactone **12** (5) (5.4 g., 0.024 mole) was heated and stirred for 4 hours at 180° with polyphosphoric acid. The mixture was poured into ice water, neutralized with ammonium hydroxide and the product extracted with chloroform and recrystallized. The products are shown in Table III.

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(4) During the course of this work, the synthesis of the 2,4-dimethyl derivative of the 3-azaketones **2c** and **3c** was described using methods similar to ours. J. Begar, G. Wolniczak and M. G. Muehlstaedt, *Z. Chem.*, 2, 274 (1962).

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