Synthesis of 1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones. I. 3-Unsubstituted Compounds

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Synthesis of 1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones *via* a Pechmann condensation of 3-carbethoxy-1-methyl-4-piperidone with various phenols is described. The limitations of this method are discussed. Synthesis of the parent ring system **3a** *via* reduction of 1,2,3,4-tetrahydro-3-(phenylmethyl)-8-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**5**) is also described.

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In connection with a project concerned with the synthesis of benzopyranopyridine bronchodilators, 3-unsubstituted-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones were needed as intermediates. A range (electron releasing, electron withdrawing, lipophilic, and lipophobic) of A-ring substituents was required to investigate the effect of various groups on biological activity.

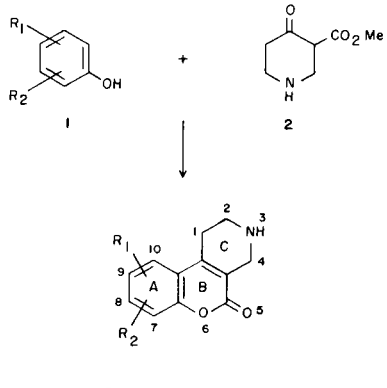
The synthesis of 8-hydroxy-3-methyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridine-5-one from resorcinol and 3-carbethoxy-1-methyl-4-piperidone *via* a Pechmann condensation has been described [1]. Two 3-unsubstituted benzopyranopyridines, synthesized using this methodology, have been described in the literature [2]. They contain 8-alkyl substituents and were used as intermediates for the synthesis of azacannabinoids. To our knowledge they are the only compounds of this type that have been described.

We have extended this synthesis to the preparation of the compounds listed in Table 1. The compounds were prepared by the condensation of 3-carbethoxy-4-piperidone hydrochloride with the corresponding phenol. The reaction works moderately well for phenols which contain an electron releasing substituent meta to the hydroxyl group. This functionality activates the para position for the initial condensation with the ketoester. The reaction is not synthetically useful for preparation of the parent compound, **3a**, and fails for phenols containing electron withdrawing substituents.

Parent compound **3a**, is a key intermediate in the synthesis of several potent bronchodilators, and thus an alternate synthesis of **3a** was required to provide the necessary amounts of material. 3-Benzyl-8-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridine-5-one (**4**) was readily available from the condensation of resorcinol with 1-benzyl-3-carbethoxy-4-piperidone. The deoxygenation of **4** to give **3a** was accomplished *via* the catalytic reduction of **5**.

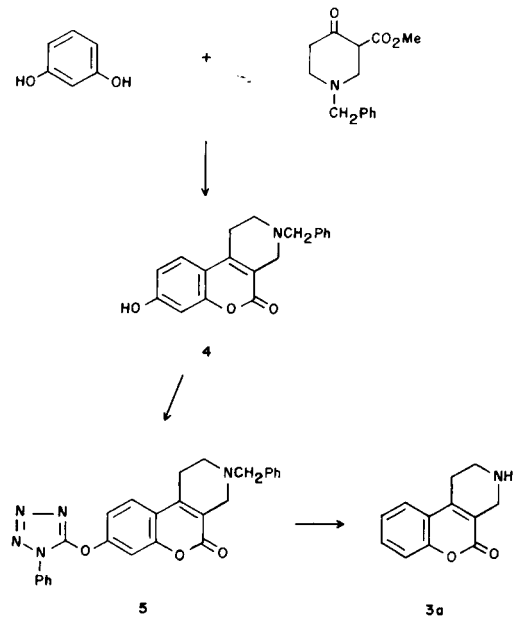
Electron releasing groups were introduced into ring A by standard aromatic chemistry. For example, **3c** was nitr-

SCHEME I

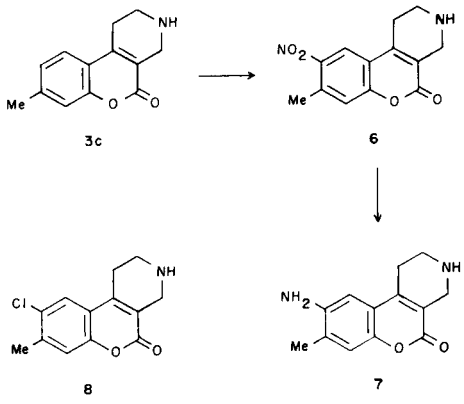


	R_1	R_2
3a	H	H
3b	H	8-OMe
3c	H	8-Me
3d	H	8-$CHMe_2$
3e	8-OMe	9-OMe
3f	8,9-O-CH_2-O	
3g	8-Me	9-Me
3h	7-OMe	8-OMe
3i	8,9,10-Tri-OMe	

SCHEME II



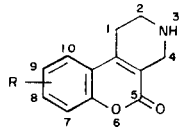
SCHEME III



ated to give mononitro compound **6**, which was converted to chloro compound **8** *via* amine **7**.

The compounds described in this paper were used as intermediates for the synthesis of several series of bronchodilators. The addition of side-chains to the 3-position of the benzopyranopyridine nucleus is described in part 2 of this series.

Table I



Compound	R	Solvent	Procedure	% Yield
3a	H	3*N* HCl	D	10
3b	8-OCH_3	EtOH	B	36
3c	8-CH_3	MeCN	A	25
3d	8-$CH(CH_3)_2$	Dil HCl	B	28
3e	8,9-Di-OCH_3	MeCN	C	75
3f	8,9-OCH_2O	dil HCl	B	47
3g	8,9-Di-CH_3	2-MeO-EtOH	B	84
3h	7,8-Di-OCH_3	MeOH/HCl	C	42
3i	8,9,10-Tri-OCH_3	dil HCl	B	62

EXPERIMENTAL

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. The nmr spectra were recorded on a Varian EM 390 at 90 MHz with TMS as internal standard. Infrared spectra were recorded on a Beckman IR-9 or IR-7 prism grating instrument or a Digital FTS-14 interferometer. Ultraviolet spectra were recorded on a Cary Model-118 spectrophotometer. High pressure liquid chromatographic separations were obtained using a Waters Prep-500 with silica columns.

Procedure A.

An 80% sulfuric acid solution (80 ml) was stirred and cooled in an ice bath, and the phenol (0.10 mole) was added, followed at once by methyl 4-oxo-3-piperidine carboxylate hydrochloride (0.10 mole). The mixture was allowed to warm to room temperature. After 48 hours the solution was poured into ice water (400 ml) and stirred until a crystalline precipitate was formed. Concentrated ammonium hydroxide was added until the mixture was strongly basic. After one hour the precipitate was filtered off, rinsed with concentrated ammonium hydroxide, then water, and dried. Recrystallization (Table I) gave pure material. Compound **3c**, prepared by this method shows typical spectral data.

1,2,3,4-Tetrahydro-8-methyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one.

Compound **3c** had uv (methanol): max 313 (10,420), 284 (10,070); ir (potassium bromide): 3200 cm^{-1}, (N-H), 1715 cm^{-1}, (CO); nmr (dimethylsulfoxide): δ 7.50 (d, 1, ArH), 7.10 (m, 2, ArH), 3.52 (s, 2, CH_2), 2.97 (t, 2, CH_2), 2.67 (m, 3, NH, and CH_2), 2.40 (s, 3, CH_3).

Procedure B.

A mixture of the phenol (0.91 mole) and methyl 4-oxo-3-piperidinecarboxylate hydrochloride (0.65 mole) was treated over one hour at 0-5° with 600 ml of 72% sulfuric acid. The mixture was stirred at room temperature for 48-72 hours, then 1.0 kg of ice/water was added, followed by enough concentrated ammonium hydroxide to raise the *p*H of the mixture to 9.0. The crude product was filtered off, stirred briefly in 1.0 ℓ of 2.5% aqueous sodium hydroxide and refiltered. Recrystallization (Table I) gave pure material.

Procedure C.

The method described in Procedure B was followed except that the phenol (0.40 mole) was added in one portion to an ice-cooled mixture of ethyl 4-oxo-3-piperidinecarboxylate hydrochloride (0.36 mole) and 200 ml of 72% sulfuric acid. Recrystallization (Table I) gave pure material.

Procedure D.

A mixture of phenol (18.8 g, 0.2 mole) and 3-carbethoxy-4-piperidone hydrochloride (20.7 g, 0.1 mole) was cooled in an ice bath and treated with 72% sulfuric acid (75 ml). The mixture was stirred at ambient temperature for four days, then an additional protion of phenol (10 g, 0.1

Analytical Data

		Analysis							
		Calcd.				Found			
Compound	Formula	C	H	N	Cl	C	H	N	Cl
3a	$C_{12}H_{11}NO_2 \cdot HCl$	60.64	5.09	5.89	14.92	60.87	5.08	5.78	14.69
3b	$C_{13}H_{13}NO_3$	67.52	5.67	6.06		67.26	5.75	6.07	
3c	$C_{13}H_{13}NO_2$	72.54	6.09	6.51		72.28	6.15	6.46	
3d	$C_{15}H_{17}NO_2 \cdot HCl \cdot 0.5\ H_2O$	62.39	6.63	4.85	12.28	62.35	6.80	4.80	12.23
3e	$C_{14}H_{15}NO_4$	64.36	5.79	5.36		64.35	5.69	5.49	
3f	$C_{13}H_{11}NO_4 \cdot HCl$	55.43	4.29	4.97	12.59	55.32	4.39	4.79	12.59
3g	$C_{14}H_{15}NO_2$	73.34	6.59	6.11		73.04	6.45	6.03	
3h	$C_{14}H_{15}NO_4 \cdot HCl$	64.36	5.79	5.36		64.14	5.74	5.23	
3i	$C_{15}H_{17}NO_5 \cdot HCl \cdot 0.8\ H_2O$	52.65	5.77	4.09	10.36	52.89	5.74	4.16	10.67

mole) was added. After five days another portion of phenol (10 g, 0.1 mole) was added and stirring continued for one more day. The mixture was then treated with ice (100 g) and concentrated ammonium hydroxide was added to adjust the *p*H to 8-9. The resultant gum was stirred in chloroform (100 ml) for 30 minutes and then filtered. The filtrate was evaporated and the residue triturated first with petroleum ether and then with diethyl ether. Crystallization (Table I) gave pure material.

1,2,3,4-Tetrahydro-8-hydroxy-3-(phenylmethyl)-5*H*-[1]benzopyrano[3,4-*c*]-pyridin-5-one (**4**).

A mixture of resorcinol (22 g, 0.2 mole) and 1-benzyl-3-carbethoxy-4-piperidone hydrochloride (59.6 g, 0.2 mole) was cooled in an ice bath and treated over one hour with 72% sulfuric acid (200 ml). The mixture was stirred at room temperature for 64 hours. Ice water (400 g) was then added, followed by concentrated ammonium hydroxide, until the *p*H of the mixture was 9.0. The crude product was filtered off, stirred briefly in 2.5% aqueous sodium hydroxide (350 ml), refiltered, and dried. The product (55 g) was converted to 1,2,3,4-tetrahydro-3-(phenylmethyl)-8-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one without further purification.

1,2,3,4-Tetrahydro-3-(phenylmethyl)-8-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**5**).

A mixture of 1,2,3,4-tetrahydro-8-hydroxy-3-(phenylmethyl)-5*H*-[1]-benzopyrano[3,4-*c*]pyridin-5-one (15 g, 0.049 mole), 5-chloro-1-phenyl-1*H*-tetrazole (9 g, 0.0498 mole), and potassium carbonate (30 g) in DMF (250 ml) was heated at 85-95° for five hours. The reaction mixture was cooled and poured over ice water, and allowed to stand at room temperature overnight. The solid was collected by filtration and rinsed with water. Recrystallization from ethyl acetate gave the pure product (10.1 g), mp 165-166°. The compound had uv (methanol): max 310 (11,964), 271 (10,745); ir (potassium bromide): 1728 cm^{-1}, (CO); nmr (dimethylsulfoxide): δ 7.9-7.4 (m, 8, ArH), 7.22 (s, 5, ArH), 3.67 (s, 2, CH_2), 3.25 (s, 2, CH_2) and 3.0-2.6 (m, 4, CH_2).

Anal. Calcd. for $C_{26}H_{21}N_5O_3$: C, 69.17; H, 4.69; N, 15.51. Found: C, 68.95; H, 4.95; N, 15.32.

1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**3a**).

A solution of 1,2,3,4-tetrahydro-3-(phenylmethyl)-8-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (21.3 g, 0.047 mole) in acetic acid (210 ml) was hydrogenated at room temperature and 50 psi in the presence of 20% palladium on carbon until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure. The residue was dissolved in water (300 ml) and made strongly basic by the addition of concentrated ammonium hydroxide. The precipitate was filtered off, rinsed with water and dried. Recrystallization from ethyl acetate gave the product (6.1 g), mp 125-128°. The compound had uv (methanol): max 308 (7,345), 280 (shoulder), 272 (10,122); ir (potassium bromide): 1702 cm^{-1}, (CO); nmr (dimethylsulfoxide): δ 7.8-7.2 (m, 4, ArH), 3.2-2.6 (m, 7, CH_2 and NH).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.32; H, 5.54; N, 7.26.

1,2,3,4-Tetrahydro-8-methyl-9-nitro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**6**).

A stirred suspension of 1,2,3,4-tetrahydro-8-methyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (9.9 g, 0.046 mole) in 10 ml of water was cooled to 5° in an ice bath. Concentrated sulfuric acid (25 ml) was added followed after 15 minutes by the dropwise addition of concentrated nitric acid (12 ml). The mixture was stirred at room temperature for 48 hours, then poured over crushed ice, stirred, and made strongly basic by the addition of concentrated ammonium hydroxide. The precipitate was filtered, rinsed with water, and dried. Recrystallization from acetonitrile gave the product (8.7 g, 73%), mp 197-199°. The compound had uv (methanol): max 262 (22,340) and 314 (7030); ir (potassium bromide): 1725 cm^{-1} (CO): nmr (dimethylsulfoxide): δ 8.20 (s, 1, ArH), 7.46 (s, 1, ArH), 3.56 (s, 2, CH_2), 3.05-2.8 (m, 2, CH_2), 2.8-2.55 (m, 2, CH_2), and 2.59 (s, 3, CH_3).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.61; H, 4.68; N, 11.04.

9-Amino-1,2,3,4-tetrahydro-8-methyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**7**).

A solution of 1,2,3,4-tetrahydro-8-methyl-9-nitro-5*H*-[1]benzopyrano-[3,4-*c*]pyridin-5-one (6.0 g, 0.023 mole) in *N,N*-dimethylformamide (100 ml) and methanol (50 ml) was hydrogenated at 50 psi in the presence of Raney Nickel (0.5 g) at room temperature for 20 hours. Additional Raney Nickel (0.5 g) in *N,N*-dimethylformamide (50 ml) was then added and hydrogenation resumed until uptake ceased. The catalyst was filtered off and rinsed with warm *N,N*-dimethylformamide. The filtrate was concentrated under reduced pressure and filtered to afford the product (4.3 g, 81%), mp 283-284°. The compound had uv (methanol): max 240 (21,875), 285 (10,408) and 355 (5,020); ir (potassium bromide): 3410 cm^{-1}, 3320 cm^{-1} (NH), 1675 cm^{-1} (CO); nmr (trifluoroacetic acid): 7.92 (bs, 2, NH_2), 7.84 (s, 1, ArH), 7.57 (s, 1, ArH), 4.54 (bs, 2, CH_2), 3.47 (bs, 2, CH_2), and 2.67 (s, 3, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.56; H, 6.37; N, 12.18.

9-Chloro-1,2,3,4-tetrahydro-8-methyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**8**).

Concentrated hydrochloric acid (8 ml) was added to a stirred suspension of 9-amino-1,2,3,4-tetrahydro-8-methyl-5*H*-[1]benzopyrano[3,4-*c*]-pyridin-5-one (1.5 g, 0.0065 mole) in water (5 ml). The solution was cooled to −5° and a solution of sodium nitrite (0.45 g, 0.0065 mole) in water (4 ml) was added dropwise. After 15 minutes the mixture was added to a solution of freshly prepared cuprous chloride (0.8 g, 0.008 moles) in 20% hydrochloric acid (8 ml) and stirred for 15 minutes. The suspension was warmed on a steam bath for one hour, allowed to cool, and made basic by addition of 10% aqueous potassium carbonate. The precipitate was filtered off, rinsed with water, dissolved in warm dilute hydrochloric acid, filtered, and reprecipitated by the addition of concentrated ammonium hydroxide. The product was collected by filtration and dried. Recrystallization from ethyl acetate gave the pure product (0.8 g, 49%), mp 184-185°. The compound had uv (methanol): max 274 (10,737) and 318 (8,640); ir (potassium bromide): 1705 cm^{-1} (CO); nmr (dimethylsulfoxide): 7.57 (s, 1, ArH), 7.30 (s, 1, ArH), 3.50 (bs, 2, CH_2), 2.94 (bs, 2, CH_2), 2.67 (bs, 2, CH_2), 2.38 (s, 3, CH_3).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61; Cl, 14.20. Found: C, 62.38; H, 4.86; N, 5.70; Cl, 14.18.

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