Synthesis of 1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones. II. Substitution at the 3-Position with 2-Aminoethyl and 2-Aminopropyl Side Chains

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Methods for the synthesis of 3-[2-aminoethyl]-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones and 3-[2-aminopropyl]-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones are described. The scope and limitations of the various methods are discussed.

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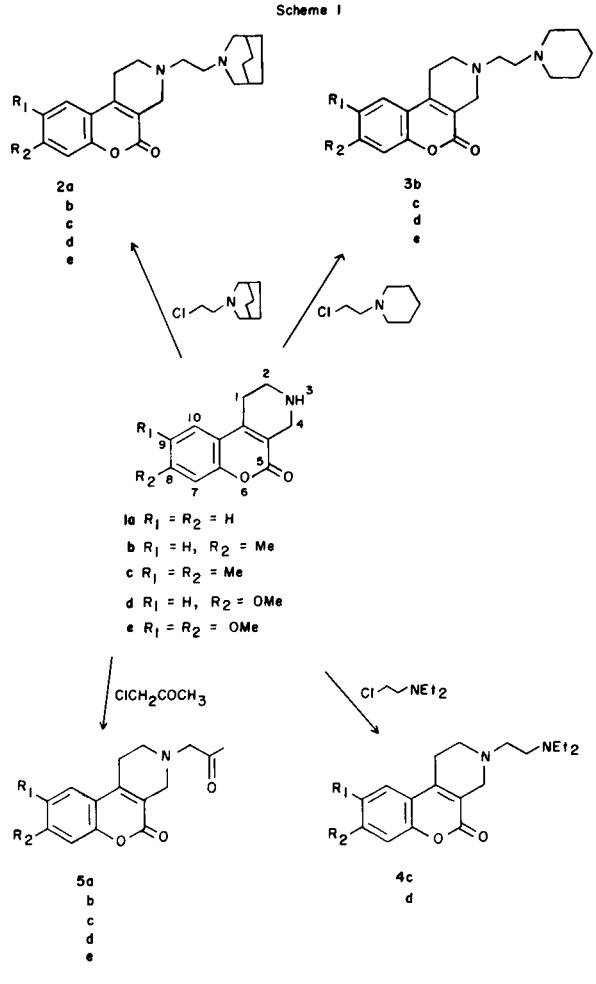
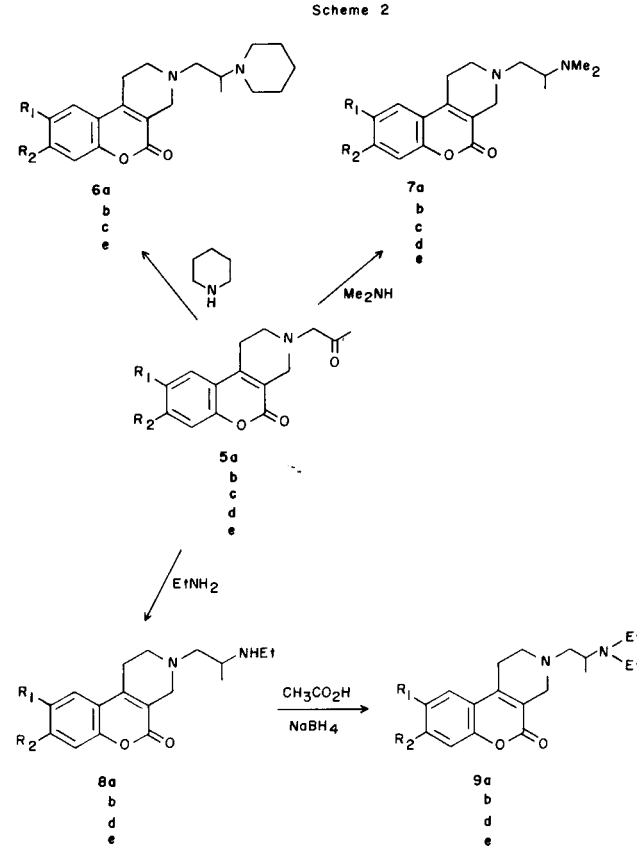
In part I [1] of this series, the synthesis of 3-unsubstituted-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones **1** was described. In this paper we describe the addition of various side-chains to the 3-position of the benzopyranopyridine nucleus. Many of the compounds, prepared by these methods, are potent bronchodilators and have the potential to be useful in the treatment of asthma and bronchitis.

Scheme I



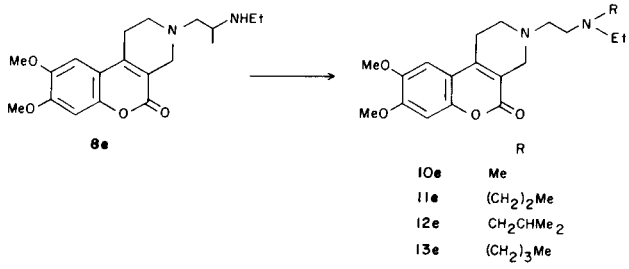
The environment of the side-chain nitrogen is one of the factors which has a critical effect on biological activity in these series of compounds. In order to delineate this effect and find molecules with optimum activity, compounds **2-4** and **6-13** (Schemes I, II, and III) in which steric congestion around the side-chain nitrogen varies considerably, were prepared.

Scheme 2



1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones **1** were alkylated with 3-(2-chloroethyl)-3-azabicyclo-[3.2.2]nonane, *N*-(2-chloroethyl)piperidine and *N*-(2-chloroethyl)diethylamine to give diamines of types **2**, **3**, and **4**

Scheme 3

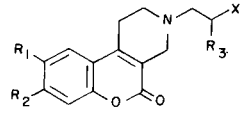


respectively. Diamines, **6** and **7**, could not be prepared by direct alkylation of **1** with the corresponding chloroalkylamines due to the formation of an intermediate aziridinium ion [2] which led to scrambling of the side-chain methyl groups between the α and β positions. To circumvent this problem, **1** was reacted with chloroacetone to give ketones, **5**. Reductive alkylation of **5** with piperidine or dimethylamine gave diamines **6** and **7** respectively. This reaction worked well for the relatively unhindered amines, dimethylamine, piperidine, and pyrrolidine, but gave a very poor yield with diethylamine.

The diethylamine analogues, **9**, were prepared *via* a two-step process from ketones, **5**. Reductive amination of **5** with ethylamine gave **8**. Treatment of **8** with acetic acid and sodium borohydride [3] gave **9**. this reaction was also carried out using formaldehyde, propionic acid, 2-methylpropionic acid, and butyric acid instead of acetic acid to give compounds **10e, 11e, 12e**, and **13e** (Scheme III) respectively.

The compounds prepared by these methods are listed in

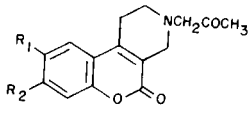
Table I



No.	R_1	R_2	R_3	X	Mp °C	Yield %	Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
2a	H	H	H	3-azabicyclo[3,2.3]non-3-yl-	267	55	$C_{22}H_{28}N_2O_2 \cdot HCl \cdot 1/5H_2O$	67.32	7.55	7.14	67.33	7.19	7.15
2b	H	Me	H	3-azabicyclo[3,2.3]non-3-yl-	155-157	50	$C_{23}H_{30}N_2O_2$	75.37	8.25	7.64	75.05	8.21	7.42
2c	Me	Me	H	3-azabicyclo[3,2.3]non-3-yl-	174-175	46	$C_{24}H_{32}N_2O_2$	75.75	8.48	7.36	75.59	8.43	7.20
2d	H	MeO	H	3-azabicyclo[3,2.3]non-3-yl-	265-270	51	$C_{23}H_{30}N_2O_3 \cdot 2HCl$	60.66	7.03	6.15	60.24	7.19	5.98
2e	MeO	MeO	H	3-azabicyclo[3,2.3]non-3-yl-	229-234	41	$C_{24}H_{32}N_2O_4 \cdot 2HCl$	59.38	7.06	5.62	59.19	7.02	5.77
3b	H	Me	H	piperidino-	277 dec	50	$C_{20}H_{26}N_2O_2 \cdot HCl$	66.19	7.50	7.72	66.18	7.56	7.63
3c	Me	Me	H	piperidino-	142-145	80	$C_{21}H_{28}N_2O_2$	74.08	8.29	8.23	73.99	8.41	8.26
3d	H	MeO	H	piperidino-	260-264	57	$C_{20}H_{26}N_2O_3 \cdot 2HCl \cdot 1/2MeOH$	57.83	6.75	6.75	57.07 [a]	6.96	6.49
3e	MeO	MeO	H	piperidino-	233-239	79	$C_{21}H_{28}N_2O_4 \cdot 2HCl$	56.63	6.79	6.29	56.37	6.99	6.24
4c	Me	Me	H	diethylamino-	261-262	57	$C_{20}H_{28}N_2O_2 \cdot 2HCl$	59.85	7.53	6.98	59.48	7.57	6.97
4d	H	MeO	H	diethylamino-	225-227	40	$C_{19}H_{26}N_2O_3 \cdot 2HCl \cdot H_2O$	55.34	7.09	6.79	55.17	7.03	6.69
6a	H	H	Me	piperidino-	118 dec	32	$C_{20}H_{26}N_2O_2 \cdot 2HCl \cdot H_2O$	57.55	7.25	6.71	57.29	7.47	6.49
6b	H	Me	Me	piperidino-	249 dec	44	$C_{21}H_{28}N_2O_2 \cdot 2HCl \cdot 4/5H_2O$	58.96	7.45	6.55	58.83	7.58	6.40
6c	Me	Me	Me	piperidino-	105-107	64	$C_{22}H_{30}N_2O_2$	74.54	8.53	7.90	74.36	8.44	7.81
6e	MeO	MeO	Me	piperidino-	105-109	28	$C_{22}H_{30}N_2O_4$	68.37	7.82	7.25	68.08	8.09	7.11
7a	H	H	Me	dimethylamino-	241 dec	75	$C_{17}H_{22}N_2O_2 \cdot 2HCl \cdot 7/10H_2O$	54.90	6.88	7.53	54.88	6.72	7.29
7b	H	Me	Me	dimethylamino-	224 dec	35	$C_{18}H_{24}N_2O_2 \cdot 2HCl \cdot 7/10H_2O$	56.02	7.16	7.26	55.91	7.34	7.09
7c	Me	Me	Me	dimethylamino-	105-107	5	$C_{19}H_{26}N_2O_2$	72.58	8.33	8.91	72.17	7.96	8.70
7d	H	MeO	Me	dimethylamino-	240-245	72	$C_{18}H_{24}N_2O_3 \cdot 2HCl \cdot 1\frac{1}{2}H_2O$	52.49	6.93	6.80	52.38	7.14	6.57
7e	MeO	MeO	Me	dimethylamino-	201-205	41	$C_{19}H_{26}N_2O_4 \cdot 2HCl$	54.92	6.73	6.68	54.57	6.89	6.77
8a	H	H	Me	ethylamino-	104-105	53	$C_{17}H_{22}N_2O_2$	71.30	7.74	9.78	71.22	7.52	9.53
8b	H	Me	Me	ethylamino-	120-121	83	$C_{18}H_{24}N_2O_2$	71.97	8.05	9.33	71.74	8.28	9.25
8d	H	MeO	Me	ethylamino-	97-100	43	$C_{18}H_{24}N_2O_3$	68.33	7.65	8.85	68.25	7.41	8.80
8e	MeO	MeO	Me	ethylamino-	210 dec	48	$C_{19}H_{26}N_2O_4 \cdot 2HCl \cdot 1/2H_2O$	53.27	6.82	6.54	53.25	6.74	6.48
9a	H	H	Me	diethylamino-	234 dec	79	$C_{19}H_{26}N_2O_2 \cdot 2HCl \cdot 4/5H_2O$	56.80	7.43	6.97	56.83	7.24	6.85
9b	H	Me	Me	diethylamino-	254 dec	50	$C_{20}H_{28}N_2O_2 \cdot 2HCl$	59.85	7.64	6.98	59.53	7.77	6.84
9d	H	MeO	Me	diethylamino-	83-85	58	$C_{20}H_{28}N_2O_3$	69.74	8.19	8.13	69.42	7.99	8.04
9e	MeO	MeO	Me	diethylamino-	205 dec	54	$C_{21}H_{30}N_2O_4 \cdot 2HCl \cdot 4/5H_2O$	54.61	7.33	6.07	54.63	7.26	6.00
10e	MeO	MeO	Me	ethylmethylamino-	182 dec	46	$C_{20}H_{28}N_2O_4 \cdot 2HCl \cdot 3/4H_2O$	53.75	7.10	6.27	53.95	7.07	6.08
11e	MeO	MeO	Me	ethylpropylamino-	93-96	38	$C_{22}H_{32}N_2O_4$	68.01	8.30	7.21	67.66	8.22	7.23
12e	MeO	MeO	Me	ethylisobutylamino-	108-111	30	$C_{23}H_{34}N_2O_4$	68.63	8.51	6.96	68.31	8.18	7.16
13e	MeO	MeO	Me	ethylbutylamino-	108-111	20	$C_{23}H_{34}N_2O_4$	68.63	8.51	6.96	68.38	8.24	6.86

[a] This is the best analysis available for carbon after repeated analyses.

Table II



No.	R_1	R_2	Mp °C	Yield %	Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
5a	H	H	128-130	58	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	69.70	6.11	5.46
5b	H	Me	128-129	76	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	70.64	6.36	4.97
5c	Me	Me	136-138	63	$C_{17}H_{19}NO_3$	71.56	6.71	4.91	71.18	6.60	4.66
5d	H	MeO	123-125	55	$C_{16}H_{17}NO_4$	66.88	5.96	4.88	66.50	6.06	4.83
5e	MeO	MeO	171-173	86	$C_{17}H_{19}NO_5$	64.34	6.04	4.41	64.43	6.08	4.58

Table I. Thus, the variety of synthetic routes, described above, provided us with the various 3-substituted benzopyranopyridines required for our bronchodilator project. Reports describing the biological properties of these compounds will be published elsewhere.

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.

General Procedure for the Synthesis of Diamines **2**, **3**, and **4**. 3-[2-(3-Azabicyclo[3.2.2]non-3-yl)ethyl]-1,2,3,4-tetrahydro-8-methoxy-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one Dihydrochloride.

A mixture of 8-methoxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]-pyridin-5-one (2.31 g, 0.01 mole), 3-(2-chloroethyl)-3-(2-azabicyclo)[3.2.2]-nonane hydrochloride (2.24 g, 0.01 mole), and triethylamine (3.03 g) in absolute ethanol (50 ml) was refluxed for 24 hours. The reaction mixture was filtered, and hydrogen chloride gas was bubbled through the filtrate. The product was filtered off, washed with ethanol and sucked dry. Recrystallization from methanol gave **2a** as a crystalline product; uv (methanol): max 309 (7,662), 272 (10,579); ir (potassium bromide): 1721 cm^{-1} (CO); nmr (dimethylsulfoxide): δ 7.8-7.2 (m, 4, ArH), 3.6-3.25 (m, 8, $-CH_2-$), 3.25-2.65 (m, 6, $-CH_2-$), 2.2-1.4 (m, 10, $-CH_2-$, -CH).

General Procedure for the Synthesis of Ketones **5**. 8,9-Dimethyl-1,2,3,4-tetrahydro-3-(2-oxopropyl)-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one.

A mixture of 8,9-dimethyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]-pyridin-5-one (30 g, 0.13 mole), 1-chloro-2-propanone (23.6 g, 0.25 mole), and triethylamine (27.3 g, 0.27 mole) in absolute ethanol (550 ml) was stirred at reflux for 21 hours. The solvent was evaporated, and the residue was partitioned between dichloromethane (700 ml) and water (500 ml). The two-phase mixture was made basic with concentrated ammonium hydroxide, the layers were separated, and the aqueous phase was extracted wtih dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated. Recrystallization of the residue from absolute ethanol gave **5c** as a crystalline product.

General Procedure for the Synthesis of Diamines **6** and **7**. 3-[2-(Dimethylamino)propyl]-1,2,3,4-tetrahydro-8,9-dimethoxy-5*H*-[1]benzopyrano-[3,4-*c*]pyridin-5-one Dihydrochloride.

A 1700 cc 316 stainless-steel autoclave was charged with 8,9-dimethoxy-1,2,3,4-tetrahydro-3-(2-oxopropyl)-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (72.47 g, 0.23 mole), methanol (400 ml), dimethylamine (112 g, 2.48 mole), 10% palladium on carbon (3.8 g)and acetic acid (2.5 ml, 0.047 mole). The reactor was sealed and agitated for 20 hours at room temperature. The vessel was then pressurized to 400 psig with hydrogen and heated to 90° with agitation. The progress of the hydrogenation was monitored by observation of the drop in pressure in a reservoir system. After five hours, the heat was turned off, and the reaction mixture was allowed to cool for 17 hours with agitation. The catalyst was removed by filtration through Super-Cel, and the filtrate was evaporated. The residue was dissolved in hot methanol, and the resulting solution was treated with excess gaseous hydrogen chloride and filtered hot. After addition of warm diethyl ether to the hot filtrate, cooling yielded **7e**, dihydrochloride. The product was filtered off and washed with cold acetone; uv (methanol): max 338 (13,700), 280 (5500), 229 (18,400); ir (potassium bromide): 1698 cm^{-1} (CO); nmr (dimethylsulfoxide): δ 7.14 (d, 2, ArH), 4.18 (bs, 2, $-CH_2-$), 3.88 (s, 6, OCH_3), 3.8-3.2 (m, 7, $-CH_2-$, -CH), 2.74 (s, 6, $-CH_3$), 1.47 (d, 3, $-CH_3$).

General Procedure for the Synthesis of Diamines **8**. 3-[2-(Ethylamino)-propyl]-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one.

A mixture of 1,2,3,4-tetrahydro-3-(2-oxopropyl)-5*H*-[1]benzopyrano-[3,4-*c*]pyridin-5-one (18.2 g, 0.071 mole), ethylamine (10 ml, 0.153 moles), anhydrous calcium sulfate (15 g), and glacial acetic acid (1 ml) in tetrahydrofuran (450 ml) was shaken at 40° in a pressure vessel. After 18 hours the mixture was cooled and filtered. The filtrate was hydrogenated at 25° and 50 psi in the presence of 10% platinum on carbon until hydrogen uptake ceased. The catalyst was removed by filtration, and the filtrate evaporated under reduced pressure. Recrystallization of the residue from ethyl acetate gave the product, **8a**; uv (methanol): max 308 (7790), 271 (10,195); ir (potassium bromide): 1715 cm^{-1} (CO); nmr (dimethylsulfoxide): δ 7.7-7.2 (m, 4, ArH), 3.30 (s, 2, $-CH_2-$), 3.0-2.2 (m, 10, $-CH_2-$, -CH, NH), 1.0 (t, 6, $-CH_3$).

General Procedure for the Synthesis of Diamines **9** to **13**. 3-[2-(Diethylamino)propyl]-1,2,3,4-tetrahydro-8-methoxy-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one.

A solution of 3-[2-(ethylamino)propyl]-1,2,3,4-tetrahydro-8-methoxy-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (3.0 g, 0.009 mole) in glacial acetic acid (20 ml) was heated to 55° under nitrogen. Sodium borohydride (2.5 g, 0.066 mole) was added portionwise. The resulting mixture was stirred, heated for 20 hours, cooled, diluted with ice-water (150 ml), made basic by the addition of concentrated ammonium hydroxide, and extracted with dichloromethane (3 × 75 ml). The combined extracts were dried over magnesium sulfate and evaporated under reduced pressure to give a crystalline product. Recrystallization from isopropyl ether gave **9d**; uv (methanol): max 320 (16,637), 250 (2,583); ir (potassium bromide): 1700 cm^{-1}); nmr (deuteriochloroform): δ 7.36 (d, 1, ArH), 6.79 (m, 2, ArH), 3.82

(s, 3, OCH_3), 3.46 (s, 2, $-CH_2-$), 3.3-2.2 (m, 11, $-CH_2-$, -CH), 1.06 (t, 9, CH_3).

Acknowledgement.

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REFERENCES AND NOTES

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