[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW MEXICO]

Cinnoline Chemistry. VI. Basic Esters, Ethers, and Amides[1,2]

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Seven new basic esters and five new basic amides have been prepared from cinnoline-4-carboxoyl chloride and the corresponding tertiary amino alcohols or the corresponding primary-tertiary diamines. Eleven new tertiary aminoalkyl 4-cinnolyl ethers have been prepared from 4-chlorocinnoline and the sodium derivative of the corresponding amino alcohols. The esters, ethers, and amides are all water soluble. Salts of each of the esters, ethers, and amides have been prepared.

In other ring systems, basic esters, ethers, and amides have displayed a variety of pharmacological activities. It appeared of interest to prepare a series of basically substituted esters, ethers, and amides for pharmacological screening.

Cinnoline-4-carboxylic acid prepared by the method of Jacobs *et al.*[4] was converted into the potassium salt. Treatment of the salt with oxalyl chloride by the method of Wingfield *et al.*[5] produced cinnoline-4-carboxyoyl chloride as the free base. This was not isolated due to instability,[4] but was treated directly with the amino alcohol to produce the series of esters whose properties are listed in Table I. The esters as free bases were all soluble in water and were very hygroscopic. Upon distillation in vacuum they were decomposed; thus they were purified as salts of organic acids.

The amides were prepared by allowing the cinnoline-4-carboxoyl chloride to react with the appropriate primary-tertiary diamine. The amide free bases were all hygroscopic and water soluble. These were identified and analyzed as the picrates. The properties of the cinnoline-4-carboxamides and their salts are shown in Table II.

The ethers reported were prepared by allowing 4-chlorocinnoline to react with the sodio derivative of an amino alcohol in anhydrous benzene solution. The ether linkage in this series is sensitive to mineral acid. In fact, attempts to recrystallize the hydrochloride salts from 95% ethanol resulted in cleavage of the ether. From these crystallizations 4-hydroxycinnoline was isolated. It was for this reason that the acidic *d*-tartrates were prepared in several instances. These salts were used for screening as well as for a solid derivative for identification of the free base. The ethers and their salts which were prepared are listed in Table III.

The infrared spectra of the cinnolines all possess the cinnoline ring absorption band at 6.3–6.4 μ. The infrared spectra of the amides also have an intense absorption band in the 6μ region indicative of the amide linkage. The infrared spectrum of β-dimethylaminoethyl cinnoline-4-carboxylate shows a strong ester band at 5.8 μ.

β-Dimethylaminoethyl cinnoline-4-carboxylate was inactive as an antifungal agent, in the inhibition of cholesterol biosynthesis and in tryptamine potentiation in rats. 4-Dimethylaminoethoxycinnoline had slight CNS stimulatory activity in rats but was inactive in the inhibition of cholesterol biosynthesis. 4-β-Morpholinoethoxycinnoline was inactive in both the inhibition of cholesterol biosynthesis and in the plasma cholesterol lowering test. 4-[γ-(*N*-Methylpiperazino)propoxy]cinnoline had slight CNS depressant activity in rats. γ-Dimethylaminopropyl cinnoline-4-carboxamide was inactive in the tryptamine potentiation in rats. γ-Piperidinopropyl cinnoline-4-carboxamide was inactive as a CNS depressant and γ-diethylaminopropyl cinnoline-4-carboxamide was inactive as an antifungal agent. Screening data on the other compounds are not available.

EXPERIMENTAL[6]

Cinnoline-4-carboxylic acid. This compound was prepared by the method of Jacobs *et al.*[4]

Potassium cinnoline-4-carboxylate. To a solution of 4.0 g. of potassium carbonate in 50 ml. of water was added 10.0 g. of cinnoline-4-carboxylic acid. The clear orange solution was treated with charcoal, filtered, and evaporated to dryness on the steam bath. The resultant yellow solid was ground to pass a 100 mesh sieve and dried overnight at 110°.

Preparation of the tertiary aminoalkyl cinnoline-4-carboxylates. The procedure is illustrated with the synthesis of β-dimethylaminopropyl cinnoline-4-carboxylate. These esters were isolated and analyzed as their salts because of the instability of the basic esters during vacuum distillation.

To a stirred and ice-cooled suspension of 3.0 g. of potassium cinnoline-4-carboxylate in 20 ml. of dry benzene was added a solution containing 1.9 g. of oxalyl chloride in 10 ml. of dry benzene over a period of 5 min. The reaction mixture was stirred for an additional 20 min. in an ice bath and then for 30 min. at room temperature. The mixture was then refluxed on a steam bath for 1 hr. After the mixture had cooled, 3.1 g. of dimethylaminopropanol in 10 ml. of

(1) For paper V in this series see R. N. Castle, H. Ward, N. White, and K. Adachi, *J. Org. Chem.*, **25**, 570 (1960).

(2) The authors are grateful to Dr. S. Yamada and Dr. K. Abe of the Tanabe Seiyaku Co., Ltd., Tokyo, Japan, for the carbon, hydrogen, and nitrogen analyses.

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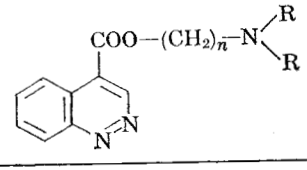
(4) T. L. Jacobs, S. Winstein, R. B. Henderson, and E. C. Spaeth, *J. Am. Chem. Soc.*, **68**, 1310 (1946).

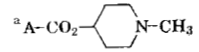
(5) H. N. Wingfield, Jr., W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **75**, 4364 (1953).

(6) All melting points are uncorrected. The infrared spectra of all the free bases were determined on a Perkin-Elmer Infracord.

TABLE I

BASIC ESTERS



n	R, R N—	Salt	M.P.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Description of Salt and Solvent Used for Crystallization
2	CH_3, CH_3 N—	Monopicrate	194–196	70	$C_{19}H_{18}N_6O_9$	48.10	3.82	17.72	48.35	3.92	17.89	Yellow needles, methanol
2	C_2H_5, C_2H_5 N—	Acidic *d*-tartrate	110–112	82	$C_{19}H_{25}O_8N_3 \cdot {}^3/_4H_2O$	52.22	6.11		52.19	6.15		Yellow rosettes, acetone
2		Acidic *d*-tartrate	119–121	68	$C_{20}H_{25}O_8N_3 \cdot 4H_2O$	47.33	6.55		47.45	6.56		Yellow prisms, acetone
2		Acidic *d*-tartrate	126–128	83	$C_{19}H_{23}O_9N_3 \cdot 1{}^1/_2H_2O$	49.13	5.64		48.73	5.90		Orange granules, ethanol
3	CH_3, CH_3 N—	Acidic *d*-tartrate	142–144	60	$C_{18}H_{23}N_3O_8 \cdot 3H_2O$	46.63	6.31		46.38	6.48		Yellow granules, ethanol
3	C_2H_5, C_2H_5 N—	Acidic *d*-tartrate	114–116	78	$C_{20}H_{27}N_3O_8$	54.91	6.22		55.24	6.19		Yellow rosettes, ethanol
		Acidic *d*-tartrate	193–195 dec.	67	$C_{19}H_{23}N_3O_8 \cdot {}^1/_4H_2O$	53.57	5.56		53.45	5.70		Yellowish green granules, ethanol

[a] A-CO_2-

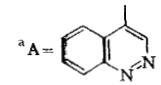
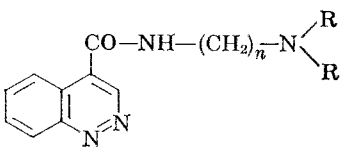
[a] A = 

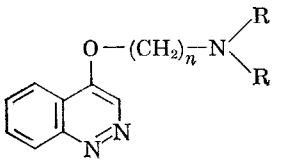
TABLE II

CINNOLINE-4-CARBOXAMIDES



n	R, R N—	B.P.	Mm.	Description	Yield, %	Salt	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Description of Salt and Solvent Used for Crystallization
3	CH_3, CH_3 N—	202–205	0.07	Solid, hygroscopic	72	Monopicrate	174–176	$C_{20}H_{21}N_7O_8$	49.28	4.34	20.12	49.12	4.45	20.44	Yellow needles, acetone
3	C_2H_5, C_2H_5 N—	210–212	0.07	Red sirup, hygroscopic	79	Monopicrate	140–142	$C_{22}H_{25}N_7O_8$	51.26	4.89	19.02	51.00	5.28	18.46	Pale yellow needles, acetone
3		224–227	0.02	Red sirup	56	Monopicrate	196–198	$C_{23}H_{25}N_7O_8$	52.37	4.73	18.58	52.27	4.27	18.30	Yellow needles, acetone
3		245–248	0.025	Red sirup	60	Monopicrate	181–184	$C_{22}H_{23}N_7O_9$	49.90	4.38	18.51	49.48	4.63	18.14	Yellow needles, acetone
2	C_2H_5, C_2H_5 N—	210–214	0.02	Red sirup	64	Monopicrate	148–150	$C_{21}H_{23}N_7O_7$	50.29	4.62		49.95	4.72		Yellowish green needles, acetone and ethanol

TABLE III. ETHERS AND SALTS



n	R, R'N—	B.P.	Mm.	Description	Yield, %	Salt	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Description of Salt and Solvent Used for Crystallization
2	CH_3, CH_3N—	162–167	0.05	Solid, m.p. 76–77°	83	Acidic *d*-tartrate	129–131	$C_{16}H_{21}N_3O_7 \cdot 1^1/_2H_2O$	48.72	6.14	10.67	48.48	6.40	10.67	Colorless needles, methanol
2	C_2H_5, C_2H_5N—	154–160	0.08	Red sirup	88	Acidic *d*-tartrate	131–133	$C_{18}H_{25}N_3O_7 \cdot {}^1/_2H_2O$	53.45	6.48	10.39	53.06	6.38	10.53	Cream granules, ethanol
2	N—	170–178	0.065	Red sirup	77	Acidic *d*-tartrate	128–131	$C_{19}H_{25}N_3O_7 \cdot H_2O$	53.64	6.40	9.87	53.41	6.87	10.11	Cream rosettes, ethanol
2	O, N—	205–210	0.02	Red sirup	75	Acidic *d*-tartrate	170–171	$C_{18}H_{23}N_3O_8$	52.80	5.66	10.26	53.07	5.94	10.41	Cream rosettes, ethanol
2	CH_3–N, N	205–208	0.04	Red sirup	68	Dipicrate	230–232	$C_{27}H_{26}N_{10}O_{15}$	44.38	3.58	19.17	44.52	3.43	18.64	Yellow leaves, acetone
3	CH_3, CH_3N—	151–153	0.01	Red sirup	90	Dipicrate	160–162	$C_{25}H_{23}N_9O_{15}$	43.54	3.36	18.28	43.97	3.52	18.13	Yellow needles, acetone
3	C_2H_5, C_2H_5N—	164–169	0.05	Red sirup	78	Acidic *d*-tartrate	190–193 dec.	$C_{19}H_{27}N_3O_7$	55.74	6.64		55.65	6.48		Cream needles, ethanol
3	N—	177–181	0.02	Semisolid	56	Acidic *d*-tartrate	166–168	$C_{20}H_{27}N_3O_7$	56.99	6.45		57.14	6.27		Cream needles, ethanol
3	CH_3–N, N—	195–198	0.01	Red sirup	80	Tripicrate	243–245 dec.	$C_{34}H_{31}N_{13}O_{22}$	41.93	3.21	18.70	41.64	3.36	18.86	Yellow needles, acetone
	[a]A–O–CH_2–CH(CH_3)–CH_2–N, N–CH_3	193–196	0.02	Red sirup	87	Dipicrate	213–215	$C_{29}H_{30}N_{10}O_{15} \cdot 2H_2O$	43.83	4.06	17.62	44.14	3.85	17.19	Yellow needles, acetone
	A–O–, N–CH_3	178–181	0.02	Solid, m.p. 88–90°	88	Dipicrate	192–194	$C_{26}H_{23}N_9O_{15}$	44.56	3.30		44.75	3.27		Yellowish green needles, acetone
	[a]A=														

dry benzene was added and the mixture refluxed for 3 hr. on the steam bath. The cooled mixture was diluted with benzene, filtered with charcoal, and evaporated under reduced pressure. The residue (*ca.* 2.8 g.) was dissolved in 8 ml. of commercial absolute ethanol and to this solution was added 1.6 g. of *d*-tartaric acid. This was dissolved by heating until the solution was clear. After standing in the refrigerator, there was obtained 3.9 g. (60%) of a yellow crystalline solid, m.p. 140–142°. Upon recrystallization from commercial absolute ethanol, fine yellow granules separated, m.p. 142–144°.

β-Dimethylaminoethyl cinnoline-4-carboxylate. After cooling the acid chloride mixture as prepared above, a solution of 5.5 g. of dimethylaminoethanol in 10 ml. of dry benzene was added and the mixture heated and stirred on the steam bath for 2 hr. The cooled mixture was diluted with ether, treated with charcoal, and filtered. After evaporation of the solvents, there was obtained 4.86 g. (70%) of a red sirup, boiling at 165–173° at 0.073 mm.

Monopicrate, m.p. 194–196°, yellow needles from methanol.

Anal. Calcd. for $C_{19}H_{18}N_6O_9$: C, 48.10; H, 3.82; N, 17.72. Found: C, 48.35; H, 3.92; N, 17.89.

Preparation of the tertiary aminoalkyl cinnoline-4-carboxamides. The procedure is illustrated with the synthesis of *N*-γ-dimethylaminopropyl cinnoline-4-carboxamide. After cooling the acid chloride mixture as prepared above, 4.2 g. of γ-dimethylaminopropylamine in 10 ml. of dry benzene was added over a period of 10 min. with stirring while the reaction mixture was kept in an ice bath. The mixture was stirred for 1 hr. at room temperature. The mixture was diluted, treated with charcoal, and filtered. After evaporation of the solvents there was obtained 3.5 g. (72%) of a red sirup, boiling at 202–205° at 0.07 mm.

4-Chlorocinnoline. This compound was prepared by the method of Leonard and Boyd.[7] Since this compound is unstable,[8] it was prepared in small quantities and used immediately. It was not necessary to purify the 4-chlorocinnoline by recrystallization but it was used directly upon recovery from the dried ether solution, m.p. 74–76°.

Preparation of aminoalkoxy ethers. The procedure is illustrated with the synthesis of 4-β-dimethylaminoethoxycinnoline.

To a solution of 4.3 g. of β-dimethylaminoethanol in 34 ml. of anhydrous benzene was added 0.57 g. of metallic sodium. The reaction mixture was refluxed on a steam bath until all the sodium had dissolved. In this instance 1 hr. heating was required. After cooling the reaction mixture in an ice bath, 3.4 g. of 4-chlorocinnoline was added and the mixture refluxed for 4 hr. on a steam bath, whereupon the solution became dark red. After allowing the reaction mixture to cool, it was diluted with dry ether, filtered with charcoal, and the solution evaporated.[9] The ether residue was distilled under reduced pressure. There was obtained 3.7 g. (83%) of a red sirup, bp. 162–167° at 0.05 mm. which after standing solidified to a pale yellow solid, m.p. 70–73°C., which after recrystallization from petroleum ether (b.p. 60–90°) gave pale yellow plates, m.p. 74–76°.

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ALBUQUERQUE, N. M.

(7) N. J. Leonard and S. N. Boyd, Jr., *J. Org. Chem.*, **11**, 423 (1946).

(8) M. Busch and K. Klett, *Ber.*, **25**, 2849 (1892).

(9) The ethers were very water soluble and, thus, it was necessary to avoid the use of water in the isolation procedure in order to obtain satisfactory yields.

[CONTRIBUTION FROM WYETH LABORATORIES, INC., RESEARCH AND DEVELOPMENT DIVISION]

A New Class of Local Anesthetics: Hydroxyalkyliminobisacetamides[1]

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A series of hydroxyalkyliminobisacetamides and their esters was prepared and examined for local anesthetic action. The compounds derived from *N*-α,α-trimethylphenethylamine showed a high degree of activity, some examples being 4000 times as active as procaine. Structure-activity relationships were studied in the course of this investigation.

During an investigation of the synthesis and pharmacology of basically substituted derivatives of acetamide several hydroxyalkylaminoacetamides[2] possessed appreciable local anesthetic activity. A more critical study of one of these, *N*-methyl-*N*-α,α-dimethylphenethyl-2-hydroxyethylaminoacetamide (I), revealed that this action was not due to the acetamide, but to a trace of commingled 2-hydroxyethyliminobis[*N*-methyl-*N*-(α,α-dimethylphenethyl)acetamide] (II).

$$HOCH_2CH_2NHCH_2CON(CH_3)C(CH_3)_2CH_2C_6H_5$$

I

The preparation of the latter compound and its subsequent testing showed it to be an extremely potent local anesthetic, at least 4000 times as active as procaine.[3]

To establish the structural requirements for activity in this series a study was made of the effect of variation in sections of the molecule on activity. The compounds prepared had the general formula III, wherein X is alkyl, cycloalkyl, or

$$HO.X.N\begin{cases}CH_2\text{—}CONRR^1\\ CH_2CONR^2R^3\end{cases}$$

III

II. X = CH_2CH_2—
R = R_2 = CH_3
R_1 = R_3 = $C(CH_3)_2CH_2C_6H_5$

(1) Presented in part before the Medicinal Chemistry Section, Delaware Valley Regional Meeting, Philadelphia, Feb. 25, 1960, abstracts p. 21.

(2) W. F. Bruce and J. Seifter, U. S. Patents: (a) **2,778,834** (1957); (b) **2,856,427** (1958).

(3) J. M. Glassman, G. H. Hudyma, and J. Seifter, *J. Pharm. Exptl. Therap.*, **119**, 150 (1957).