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DIHYDROERGOT RELATIVES: QUINOLINECARBOXAMIDES AND ESTERS

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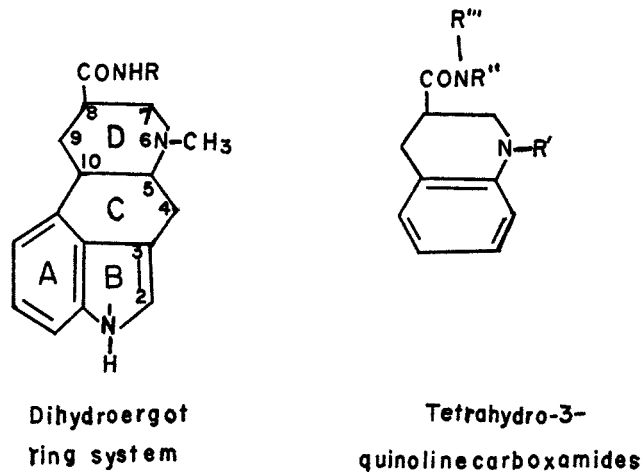
Other investigators (1–12) have made an effort to determine structure-activity relationships in the ergot series. The objective of the majority of these workers was the synthesis of compounds possessing the oxytocic properties of ergonovine. Hydrogenation of the double bond in the 9,10-position of the ergot alkaloids of the polypeptide type produces a loss in oxytocic properties and an enhancement of the cardiovascular action (13). The cardiovascular effect in which we were interested is of central origin and results in a decrease in blood pressure (14). Our aim was the construction of a simple relative of the dihydroergot alkaloids with desirable hypotensive properties. Bovet and co-workers (1, 3) have demonstrated that a number of simple tetrahydro-β-naphthylamines related to the ergot ring system possess sympatholytic properties.

Rings C and D of the dihydroergot ring system (13) (Fig. 1) may be visualized as a substituted hydrogenated 3-quinolinecarboxamide. Accordingly, a number of substituted quinolinecarboxamides, their quinolinium salts and tetrahydro derivatives were prepared in order to determine the contribution of this portion of the ergot molecule to its biological activity.

The synthesis of the various 3-quinolinecarboxamides and esters necessitated the preparation of large quantities of 3-quinolinecarboxylic acid. The method of Gilman and Spatz (15), *i. e.* quinoline → 3-bromoquinoline → 3-cyanoquinoline → 3-quinolinecarboxylic acid, was found convenient. The preparation of 3,7-quinolinedicarboxylic acid was accomplished (although in poor yield) by oxidation of 3,7-dimethylquinoline prepared by the method described by Manske (16) and Untermohlen (17).

The simple N-alkyl- and N,N-dialkyl-3-quinolinecarboxamides were prepared from 3-quinolinecarboxylic acid by condensation with the appropriate amine in the presence of phosphorus oxychloride (15). Application of this procedure using the amino acid alanine, however, was unsuccessful. The preparation of the N-(3-quinolinecarbonyl)amino acids (Table I) involved reacting 3-quinolinecarbonyl chloride (I) or its hydrochloride with the appropriate amino acid ester or its hydrochloride in the presence of a base. 3-Quinolinecarbonyl chloride has been described previously only as the hydrochloride (18). On distillation under reduced pressure, the hydrochloride readily evolves hydrogen chloride and gives the base.

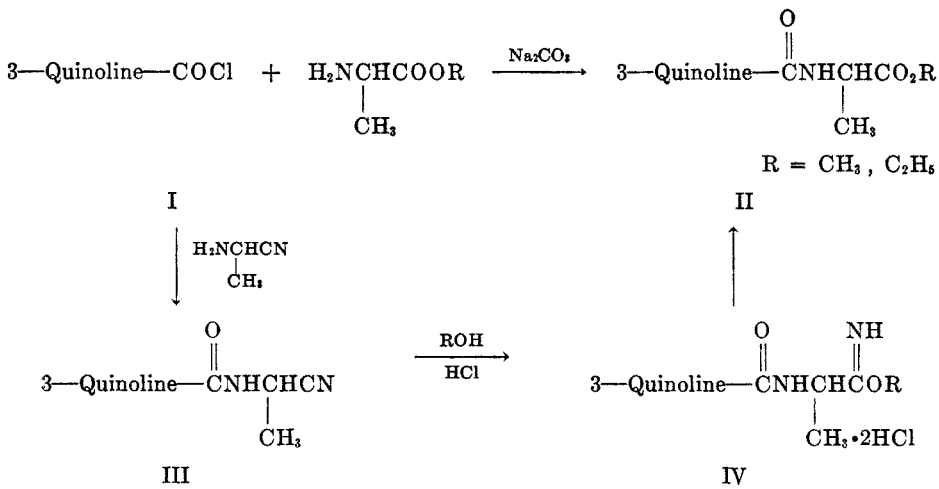
Ethyl and methyl N-(3-quinolinecarbonyl)alaninate (II, R = C_2H_5 and CH_3 respectively) also were prepared from the nitrile (III) *via* the imido ester (IV). Hydrolysis of the ester (II, R = C_2H_5) occurred satisfactorily to give the amino acid derivative (McN-275) whereas ammonolysis of the ester yielded the amide (McN-382). It was found more convenient to prepare the acid derivative by



Dihydroergot ring system

Tetrahydro-3-quinolinecarboxamides

FIG. 1



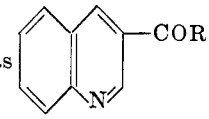
hydrolysis of the corresponding ester rather than by causing 3-quinolinecarbonyl chloride to react with the amino acid.

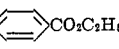
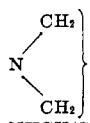
In an attempt to prepare N-(3-quinolinecarbonyl)ethylenediamine by the reaction of 3-quinolinecarbonyl chloride with an excess of ethylenediamine, only N,N′-bis-(3-quinolinecarbonyl)ethylenediamine was obtained. A similar reaction using piperazine in place of ethylenediamine gave N,N′-bis-(3-quinolinecarbonyl)piperazine.

The reaction of 3-quinolinecarbonyl chloride with an equivalent of diethyl- or dimethyl-aminoethanol gave the corresponding esters as monohydrochlorides. Blicke and Gearian (5) described the preparation of 2-diethylaminoethyl 3-quinolinecarboxylate from the acid chloride hydrochloride and isolated the compound as the dihydrochloride.

Pharmacological results. The pharmacological properties of the compounds

TABLE I

QUINOLINECARBOXAMIDES AND ESTERS 

McN. No.	R	Recrystallization Solvent	M.P., °C.	Formula	Nitrogen	
					Cal'd	Found
249	NHC_2H_5	Benzene	130–132	$C_{12}H_{12}N_2O$	14.0	13.8
255	$NHCH(CH_3)CN$	Benzene	129–130.5	$C_{13}H_{11}N_3O$	18.7	19.0
255-11	$NHCH(CH_3)CN \cdot HCl$	Methanol	228–232 dec.	$C_{13}H_{12}ClN_3O$	16.1	16.3
250-11	$NHCH(CH_3)C(OCH_3)NH \cdot 2HCl$	—	dec.	$C_{14}H_{17}Cl_2N_3O_2$	12.7	12.5
247	$NHCH(CH_3)CO_2CH_3$	Benzene	152–153.5	$C_{14}H_{14}N_2O_3$	10.9	10.9
248	$NHCH(CH_3)CO_2C_2H_5$	Benzene-heptane	108.5–109.5	$C_{15}H_{16}N_2O_3$	10.3	10.3
275	$NHCH(CH_3)CO_2H$	Methanol-water	231.5–233 dec.	$C_{13}H_{12}N_2O_3$	11.5	11.4
388	$NHCH(CH_3)CO_2C_2H_5$[a]	Pet. Ether (b.p. 35–75°)	81–83	$C_{15}H_{16}N_2O_3$	10.3	10.3
363	$NHCH_2CO_2C_2H_5$	Benzene-heptane	94–97 Clears at 113	$C_{14}H_{14}N_2O_3$	10.8	10.5
382	$NHCH(CH_3)CONH_2$	Water	226.5–228	$C_{13}H_{13}N_3O_2$	17.3	16.9
387	$NHCH(CH_2C_6H_5)CO_2C_2H_5$	Benzene-heptane	129–130	$C_{21}H_{20}N_2O_3$	8.0	7.7
416		Acetone-water	182–184	$C_{19}H_{16}N_2O_3$	8.8	8.3
417	$NHCH(CO_2C_2H_5)CH_2CH_2CO_2C_2H_5$	Benzene-heptane	96–98	$C_{19}H_{22}N_2O_5$	7.8	7.7
428	$NHCH(CH_2CH_2SCH_3)CO_2C_2H_5$	Benzene-heptane	94–96	$C_{17}H_{24}N_2O_3S$	8.4	8.7
454	$NHCH(CO_2C_2H_5)CH_2CH(CH_3)_2$	Heptane	77–79	$C_{18}H_{22}N_2O_4$	8.9	8.7
X-55-11	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	Methanol	211.5–212	$C_{16}H_{21}ClN_2O_2$	9.1	9.0
274-11	$OCH_2CH_2N(CH_3)_2 \cdot HCl$	Methanol-ether	190–191	$C_{14}H_{17}ClN_2O_2$	10.0	9.6
306	$NHCH_2$-bis	60% Acetic acid	275–277	$C_{22}H_{18}N_4O_2$[b]	15.1	14.9
278	 bis	*n*-Propanol	269–271	$C_{24}H_{20}N_4O_2$	14.1	13.8
390	$NHCH(CH_3)CO_2C_2H_5$[c]	Benzene-methanol	181–184	$C_{21}H_{28}N_2O_5$	10.1	9.9

[a] Substituent in 2-position. [b] Calc'd: C, 71.3; H, 4.9. Found: C, 71.1; H, 5.0. [c] $CONHCH(CH_3)CO_2C_2H_5$ also in 7-position.

described in this paper have been presented elsewhere (19). The 3-quinolinecarboxamide derivatives exhibit slight cardiovascular and oxytocic activity. The tetrahydro derivatives likewise have slight hypotensive activity of brief duration but are relatively strong oxytocic agents. The quinolinium salts possess relatively strong hypotensive but no oxytocic activity. The hypotensive effect of the last-mentioned group is due to a combination of histamine liberation and direct effects on the central nervous system and peripheral vasculature.

EXPERIMENTAL[1]

N-Ethyl-3-quinolinecarboxamide (*McN-249*). The procedure employed by Gilman and Spatz (15) for the preparation of N,N-diethyl-3-quinolinecarboxamide was followed. From 8 g. (0.05 mole) of 3-quinolinecarboxylic acid and 3.7 g. (0.05 mole) of ethylamine hydrochloride was obtained 6.5 g. (71%) of product, m.p. 130–132°.

Anal. Calc'd for $C_{12}H_{12}N_2O$: N, 14.0. Found: N, 13.8.

3-Quinolinecarbonyl chloride (*McN-398*). The procedure employed by Späth and Spitzer (20) for the preparation of cinchoninyl chloride was followed. A mixture of 20 g. (0.12 mole) of 3-quinolinecarboxylic acid and 50 ml. of thionyl chloride was refluxed gently for one hour. The excess thionyl chloride was evaporated off under diminished pressure and the residue was distilled at 180–182° (25 mm.) to give 21 g. (95%) of 3-quinolinecarbonyl chloride.

α-(3-Quinolinecarboxamido)propionitrile (*McN-255*). To a cold solution (0–5°) of 6.2 g. (0.06 mole) of sodium carbonate and 4.2 g. (0.06 mole) of freshly distilled α-aminopropionitrile (21) in 50 ml. of water was added gradually with stirring a solution of 11 g. (0.06 mole) of 3-quinolinecarbonyl chloride in 75 ml. of chloroform. The resulting mixture was kept at 0–10° for 18 hours. The layers were separated and the aqueous layer was extracted with chloroform. Evaporation of the chloroform and recrystallization of the residue from a benzene-heptane mixture gave 9.7 g. (72%) of α-(3-quinolinecarboxamido)propionitrile, m.p. 129–130.5°.

Anal. Calc'd for $C_{13}H_{11}N_3O$: N, 18.7 Found: N, 19.0.

A *hydrochloride* was prepared in the usual way and was recrystallized from methanol, m.p. 228–232° dec.

Anal. Calc'd for $C_{13}H_{12}ClN_3O$: N, 16.1. Found: N, 16.3.

α-(3-Quinolinecarboxamido)propionimidic acid methyl ester dihydrochloride (*McN-250*). Hydrogen chloride was passed into a cold solution (0–5°) of 1.8 g. (0.08 mole) of α-(3-quinolinecarboxamido)propionitrile in 30 ml. of methanol. α-(3-Quinolinecarboxamido)propionitrile hydrochloride immediately separated from solution and on further addition of hydrogen chloride the solid gradually dissolved. The solution was kept at 0–10° for 18 hours. The solid that separated from solution was removed, washed with dry ether, and dried in a vacuum-desiccator over solid potassium hydroxide. The product (1.8 g., 68%) decomposed on heating.

Anal. Calc'd for $C_{14}H_{17}Cl_2N_3O_2$: N, 12.7 Found: N, 12.5.

Methyl α-(3-quinolinecarboxamido)propionate (*McN-247*). A solution of 1.5 g. (0.05 mole) of α-(3-quinolinecarboxamido)propionimidic acid methyl ester dihydrochloride in 10 ml. of water was neutralized carefully with 5% sodium carbonate solution. The solid which separated from solution was removed by filtration and recrystallized from a water-methanol mixture to give 1 g. (86%) of product, m.p. 152–153.5°.

Anal. Calc'd for $C_{14}H_{14}N_2O_3$: N, 10.9 Found: N, 10.9.

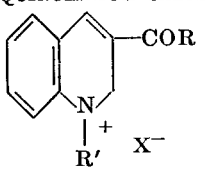
N-(3-Quinolinecarbonyl)amino acid esters (Table I). The method described for the preparation of ethyl α-(3-quinolinecarboxamido)hydrocinnamate is illustrative of the procedure employed for the preparation of the 3-quinolinecarboxamide derivatives listed in Table I, other than those described in the experimental section.

Ethyl α-(3-quinolinecarboxamido)hydrocinnamate (*McN-387*). A mixture of 3.5 g. (0.02 mole) of 3-quinolinecarboxylic acid and 25 ml. of thionyl chloride was refluxed gently for one hour. The excess thionyl chloride was evaporated off under reduced pressure and the residue was suspended in 100 ml. of dry chloroform. To this suspension, cooled in an ice bath, was added a solution of 4 g. (0.04 mole) of sodium carbonate in 50 ml. of water and a solution of 4 g. (0.02 mole) of ethyl phenylalaninate hydrochloride in 50 ml. of water, respectively. The mixture was kept at 0–10° for 18 hours. The layers were separated and the aqueous layer was extracted with chloroform. Evaporation of the chloroform and recrys-

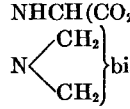
[1] All melting points are uncorrected.

TABLE II

QUINOLINIUM SALTS



McN. No.	R	R′	X	Recrystallization solvent	M.P., °C.	Formula	Nitrogen	
							Calc'd	Found
256-15	NHC_2H_5	CH_3	I	Methanol-ether	212–215	$C_{13}H_{15}IN_2O$	8.2	8.0
254-15	NHC_2H_5	C_2H_5	I	Methanol	200–202	$C_{14}H_{17}IN_2O$	7.8	7.6
251-15	$N(C_2H_5)_2$	CH_3	I	Methanol-ether	158–159	$C_{15}H_{19}IN_2O$	—	—
253-15	$N(C_2H_5)_2$	C_2H_5	I	Methanol-ether	145–148	$C_{16}H_{21}IN_2O$[a]	7.3	6.8
258-14	$NHCH(CH_3)CO_2CH_3$	CH_3	Br	Methanol-ether	194–196 dec.	$C_{15}H_{17}BrN_2O_3$	7.9	8.0
258-15	$NHCH(CH_3)CO_2CH_3$	CH_3	I	Methanol-ether	206–207	$C_{15}H_{17}IN_2O_3$	7.0	7.2
257-15	$NHCH(CH_3)CO_2C_2H_5$	C_2H_5	I	Methanol	155–157	$C_{17}H_{21}IN_2O_3$	6.5	6.2
259-14	$NHCH(CH_3)CO_2C_2H_5$	CH_3	Br	Methanol-ether	181–182.5	$C_{16}H_{19}BrN_2O_3$	7.6	7.7
259-15	$NHCH(CH_3)CO_2C_2H_5$	CH_3	I	Methanol	185–186	$C_{16}H_{19}IN_2O_3$	6.8	6.4
358-15	$NHCH(CH_3)CO_2H$	CH_3	I	Methanol-ether	122–125	$C_{14}H_{15}IN_2O_3$	7.4	7.3
359-15	$NHCH_2CO_2C_2H_5$	CH_3	I	Methanol	197–198.5	$C_{15}H_{17}IN_2O_3$	7.0	6.9
365-15	$NHCH(CH_3)CONH_2$	CH_3	I	Dimethylformamide	239–241	$C_{14}H_{16}IN_3O_2$	10.9	10.6
380-15	$NHCH(CH_3)CN$	CH_3	I	Methanol	171–172.5	$C_{14}H_{14}IN_3O$	11.4	11.0
383-15	$NHCH(CH_2C_6H_5)CO_2C_2H_5$	CH_3	I	Methanol	152–154.5	$C_{22}H_{23}IN_2O_3$	5.7	5.4
391-15	$NHCH(CH_3)CO_2C_2H_5$[b]	CH_3	I	Methanol-ether	189.5–191	$C_{22}H_{28}IN_3O_6$	7.5	7.4

418-15		CH_3	I	Methanol-water	246–248	$C_{20}H_{19}IN_2O_3$	6.1	5.9
419-11	$NHCH(CH_3)CO_2C_2H_5$	$C_6H_5CH_2$	Cl	Methanol-ether	177–179	$C_{22}H_{23}ClN_2O_3$	7.0	6.8
429-11	$NHCH(CH_3)CO_2C_2H_5$	2,5-$CH_3O(CH_3)C_6H_3CH_2$	Cl	Methanol-ether	158–158.5	$C_{24}H_{27}ClN_2O_4$	6.3	6.5
445-15	$NHCH(CO_2C_2H_5)CH_2CH(CH_3)_2$	CH_3	I	Isoamyl alcohol	130–132	$C_{19}H_{25}IN_2O_3$	6.1	6.0
464-15	$NHCH(CH_2CH_2SCH_3)CO_2C_2H_5$	CH_3	I	—	115–119[c]	$C_{18}H_{23}IN_2O_3S$	5.9	5.5
465-15	$NHCH(CO_2C_2H_5)CH_2CH_2CO_2C_2H_5$	CH_3	I	—	—[c]	$C_{20}H_{25}IN_2O_5$	5.6	5.6
465-47	$NHCH(CO_2C_2H_5)CH_2CH_2CO_2C_2H_5$	CH_3	CH_3SO_4	Methyl ethyl ketone-ether	107–110	$C_{21}H_{28}N_2O_9S$	5.8	5.7
307-15	 bis	CH_3	I	Methanol-water	293–295 dec.	$C_{26}H_{26}I_2N_4O_2$[d]	8.2	8.1
310-15	$NHCH_2$-bis	CH_3	I	Methanol-water	278–280	$C_{24}H_{24}I_2N_4O_2$	8.6	8.8

[a] Calc'd: C, 50.0; H, 5.5; I, 33.0. Found: C, 49.5; H, 5.3; I, 32.9. [b] $CONHCH(CH_3)CO_2C_2H_5$ also in 7-position. [c] Resisted recrystallization. [d] Calc'd: C, 45.9; H, 3.9; I, 37.3. Found: C, 46.3; H, 4.2; I, 36.9.

tallization of the residue from a benzene-heptane mixture gave 4.7 g. (77%) of product, m.p. 128–130°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3$: N, 8.0. Found: N, 7.7.

α-(3-Quinolinecarboxamido)propionic acid (McN-275). A mixture of 1.8 g. (0.0066 mole) of ethyl α-(3-quinolinecarboxamido)propionate and 6 ml. of 1.1 *N* (0.0066 mole) sodium hydroxide was kept at room temperature for 18 hours. The mixture was filtered and the filtrate was neutralized with an equivalent amount of 1 *N* hydrochloric acid. The resulting mixture was concentrated under diminished pressure and the solid was removed. Recrystallization of the solid from a water-methanol mixture gave 1.3 g. (81%) of product, m.p. 231.5–233° dec.

Anal. Calc'd for $C_{13}H_{12}N_2O_3$: N, 11.5. Found: N, 11.4.

α-(3-Quinolinecarboxamido)propionamide (McN-382). A mixture of 2 g. (0.0074 mole) of ethyl α-(3-quinolinecarboxamido)propionate and 50 ml. of 28% ammonium hydroxide solution was kept at room temperature for 18 hours. The resulting mixture was evaporated to dryness and the residue was recrystallized with the aid of charcoal from water to give 1.4 g. (79%) of product, m.p. 226.5–228°.

Anal. Calc'd for $C_{13}H_{13}N_3O_2$: N, 17.3 Found: N, 16.9.

3,7-Quinolinedicarboxylic acid (McN-381). To a refluxing solution of 61 g. (0.42 mole) of 3,7-dimethylquinoline (17) in 1 liter of 50% sulfuric acid were added three 100-g. (1 mole) portions of chromium trioxide at intervals of 4, 15, and 24 hours, respectively. The mixture was allowed to cool to room temperature and the solid was removed. The solid was treated with 10% sodium hydroxide solution, heated to boiling, and the mixture was filtered. The filtrate was neutralized with acetic acid. The product was removed and was recrystallized from acetic acid. There was obtained 13 g. (14%) of 3,7-quinolinedicarboxylic acid, m.p. 338–340°.

Anal. Calc'd for $C_{11}H_7NO_4$: N, 6.5. Found: N, 6.7.

Application of the above procedure to 3-methylquinoline gave a 42% yield of 3-quinolinecarboxylic acid.

2-Diethylaminoethyl 3-quinolinecarboxylate hydrochloride (McN-X-55). To a solution of 4.7 g. (0.25 mole) of 3-quinolinecarbonyl chloride in 50 ml. of dry chloroform was added 2.9 g. (0.25 mole) of freshly distilled diethylaminoethanol. The mixture was kept at room temperature for three days. The solvent was evaporated and the product (6.5 g., 86%) was recrystallized from methanol, m.p. 211.5–212°.

Anal. Calc'd for $C_{16}H_{21}ClN_2O_2$: N, 9.1. Found: N, 9.0.

2-Dimethylaminoethyl 3-quinolinecarboxylate hydrochloride (McN-274) was prepared, following the above procedure, from equivalent quantities of 3-quinolinecarbonyl chloride and dimethylaminoethanol.

Quinolinium salts. The quinolinium halides described in Table II were prepared by refluxing a solution of the quinoline derivative and an alkyl or aralkyl halide in benzene. The methobromides (McN-258-14 and 259-14) were prepared by heating a mixture of the quinoline derivative, methyl bromide, and methyl or ethyl alcohol at an elevated temperature (100°) for 14 hours. The use of methyl alcohol as a solvent in the reaction of ethyl α-(3-quinolinecarboxamido)propionate with methyl bromide at an elevated temperature produced an ester interchange and the sole product isolated was the methobromide of the methyl ester (McN-258-14).

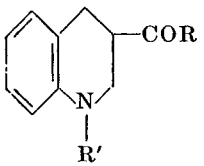
The quinolinium salts McN-464 and 465 (Table II) were hygroscopic. They were purified by dissolving in water, extracting with ether, evaporating the aqueous solution to dryness under reduced pressure, and drying the residue over phosphorus pentoxide.

The yields of the quinolinium salts ranged from 85–95%.

Tetrahydroquinolines. The preparation of the tetrahydroquinoline derivatives listed in Table III was accomplished by reduction of the corresponding quinolinium iodide at a pressure of 3 to 4 atmospheres using Adams catalyst. The reduction of 1-ethyl- (McN-257-15) and 1-methyl-3[N-(1-carbethoxyethyl)carbamyl]quinolinium iodide (McN-259-15) produced diastereoisomers which were partially separated by fractional crystalliza-

TABLE III

TETRAHYDROQUINOLINECARBOXAMIDES



McN. No.	R	R'	Recrystallization Solvent	Yield, %	M.P., °C.	B.P., °C.	MM.	Formula	Nitrogen	
									Calc'd	Found
234	NHC_2H_5	CH_3	Methanol-water	95	111–112.5	—		$C_{13}H_{18}N_2O$	12.8	12.8
238	NHC_2H_5	C_2H_5	Benzene-heptane	67	81–83	163–167	0.1	$C_{14}H_{20}N_2O$	12.1	12.1
240	$N(C_2H_5)_2$[a]	CH_3	—	49	—	148–150	0.1	$C_{15}H_{22}N_2O$	11.4	11.3
239	$N(C_2H_5)_2$	C_2H_5	—	63	—	159–160	0.2	$C_{16}H_{24}N_2O$	10.8	10.4
272-Y	$NHCH(CH_3)CO_2C_2H_5$[b, c]	CH_3	Benzene-heptane	84	144–145	—		$C_{16}H_{22}N_2O_3$	9.7	9.5
272-Z	$NHCH(CH_3)CO_2C_2H_5$[b, c]	CH_3	Benzene-heptane		95–97	—		$C_{16}H_{22}N_2O_3$	9.7	9.4
273-Y	$NHCH(CH_3)CO_2C_2H_5$[b]	C_2H_5	Heptane	77	82–84	—		$C_{17}H_{24}N_2O_3$	9.2	9.2
273-Z	$NHCH(CH_3)CO_2C_2H_5$[b]	C_2H_5	Heptane		107.5–110	—		$C_{17}H_{24}N_2O_3$	9.2	9.3
277-Z	$NHCH(CH_3)CO_2H$[d]	C_2H_5	Ether-pet. ether	38	119–121 dec.	—		$C_{17}H_{20}N_2O_3$	10.1	9.8
277-Z-11	$NHCH(CH_3)CO_2H \cdot HCl$	C_2H_5	Ether-methanol	—	203–205 dec.	—		$C_{15}H_{21}ClN_2O_3$	9.0	8.6

[a] A methiodide derivative (McN-252-15) was prepared and recrystallized from a mixture of methanol and ether, m.p. 160–161°. *Anal.* Calc'd for $C_{16}H_{25}IN_2O$; N, 7.2. Found: N, 6.8. [b] Diastereoisomer. [c] An ethiodide (McN-427-15) was prepared from a mixture of McN-272-Y and McN-272-Z and recrystallized from a methanol-ether mixture, m.p. 170–171°. *Anal.* Calc'd for $C_{18}H_{27}IN_2O_3$; N, 6.3. Found: N, 6.4. [d] Prepared by hydrolysis of a mixture of McN-273-Y and McN-273-Z.

tion. The hydrolysis of the esters listed in Table III gave products which decomposed on standing.

SUMMARY

The preparation and properties of a series of substituted quinolinecarboxamides, their quinolinium salts and tetrahydro derivatives, are described. A brief summary of their pharmacological properties is given.

The preparation and properties of two basic esters of 3-quinolinecarboxylic acid also is described.

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