NOTES

Synthesis of Potential Anticancer Agents. VII. Some 3-Chloropropionyl Amides[1-3]

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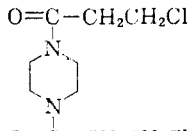
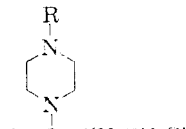
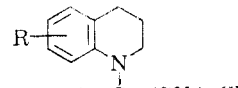
Carbon and co-workers[4] have reported anticancer activity for amides of type I. In connection with other work in progress in this laboratory we had been treating a series of haloacyl halides with piperazines, tetrahydroquinolines and other amines. In view of the interest in I, we wish now to report on some of these related amides of the general type II and III which are included in Table I.



I



II



III

Attempts to purify the oily 1-(3-chloropropionyl)-1,2,3,4-tetrahydroquinoline[5] (III, n = 2, R = H) by chromatography over alumina[6] gave on elution with benzene-ethanol (9:1) a solid of the formula $C_{12}H_{13}NO$ rather than the expected chloro compound. Similar attempts to chromatograph 1,4-bis-(3-chloropropionyl)-1,2,3,4-tetrahydroquinoxaline gave a compound $C_{14}H_{14}N_2O_2$. Loss of the elements of hydrogen chloride was also noted on alumina[6] chromatography of other 3-chloropropionyl amides as shown in Table II. Although the previously reported[5] compound IV had the same melting point as the $C_{12}H_{13}NO$ compound, direct comparison with an authentic

(1) Part VI, F. D. Popp and H. Swarz, *J. Org. Chem.*, **26**, 4764 (1961).

(2) A portion of this material was presented before the Division of Medicinal Chemistry at the 140th Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

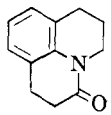
(3) This work was supported in part by research grants from the American Cancer Society (T 177) and from the National Cancer Institute, U. S. Public Health Service (CY 4814 & CY 4814C1).

(4) J. A. Carbon, S. M. Brehm, and J. S. Ratajczyk, Abstracts, American Chemical Society Meeting, March, 1961, St. Louis, Mo., p. 11-N.

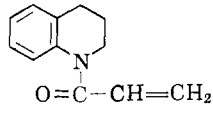
(5) P. A. S. Smith and T. Y. Yu, *J. Am. Chem. Soc.*, **74**, 1096 (1952).

(6) Merck, Reagent Grade Aluminum Oxide.

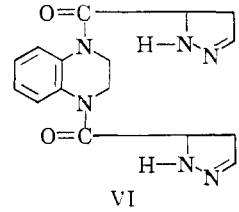
sample of IV[7] indicated that they were not the same material. Further, our chromatographed products decolorized permanganate and bromine which would not support structure IV. To confirm that



IV



V



VI

the compounds had a structure of the type V, the piperazine amide I was chromatographed over alumina[6] to give a material identical with 1,4-diacrylylpiperazine.[8] Further evidence for the unsaturated nature of the chromatographed materials was adduced by treating the quinoxaline, $C_{14}H_{14}N_2O_2$, with diazomethane to give a compound whose analysis and infrared spectrum were consistent with structure VI.

This dehydrohalogenation did not occur on acid washed alumina[9] and in fact chromatography on this latter material was an excellent method of purification for the 3-chloropropionyl amides. Chromatography of 1-(chloroacetyl)-, 1-(3-chloropropyl)-, 1-(4-chlorobutyryl)-, and surprisingly 1-(3-bromopropionyl)-1,2,3,4-tetrahydroquinoline on alumina[6] did not result in any change.

Several of the chloroacetyl and 3-chloropropionyl amides were reduced with lithium aluminum hydride to give the chloroethyl ("one-armed mustards") and chloropropylamines listed in Table III. It is of interest to note that these reductions proceeded in high yield without the loss of chlorine as might be anticipated from the alumina results.

Most of the 3-chloropropionyl amides and the "one-armed mustards" were submitted for screening against the Dunning leukemia in rats.[10] None of the compounds screened exhibited any activity when given in a dose of 250 mg./kg. to an established tumor on day 7 except I which also has been reported previously as being active.[4]

(7) We wish to thank Dr. P. A. S. Smith for an authentic sample of IV.

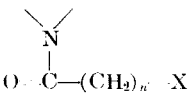
(8) We thank Dr. J. A. Carbon for the spectrum of a sample of 1,4-diacrylylpiperazine.

(9) Merck, Reagent Grade Acid Washed Aluminum Oxide.

(10) We wish to thank Drs. Ralph Jones, Jr., and Leo Rane for making the screening results available to us.

TABLE I

N-(HALOACYL)-AMIDES



Amine used	n	X	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Piperazine[a]	2	Cl	102.5–104[b,c]	87	$C_{10}H_{16}Cl_2N_2O_2$	44.96	6.04		44.83	5.97	
N-Methylpiperazine[a]	2	Cl	194[d,e]	96	$C_8H_{15}ClN_2O \cdot HCl$[f]	42.30	7.10		42.26	7.01	
			186–187[g]		$C_8H_{15}ClN_2O \cdot CH_3I$[h]	32.50	5.45		32.23	5.23	
N-Phenylpiperazine[a]	2	Cl	184–186[i]		$C_{12}H_{17}ClN_2O \cdot HCl$[j]	53.99	6.27		54.09	6.38	
			84–85[g]		$C_{13}H_{17}ClN_2O$[j]	61.78	6.78		61.65	6.79	
N-Carbethoxypiperazine[k]	2	Cl	oil	70	$C_{10}H_{17}ClN_2O_3$[l]	48.29	6.89	11.27	48.63	7.09	11.10
N-(2-Ethanol)-piperazine[m]	2	Cl	105–110		$C_9H_{17}ClN_2O_2$–$C_6H_3N_3O_7$[n]	40.05	4.48	15.57	38.92	4.68	16.10
1,2,3,4-Tetrahydroquinoxaline[o]	2	Cl	119–120[g]	82	$C_{14}H_{16}Cl_2N_2O_2$	53.34	5.12	8.89	53.51	5.42	8.69[p]
Phenothiazine	2	Cl	140[g]	73	$C_{15}H_{12}ClNOS$	62.17	4.14	4.83	62.15	4.25	4.72
Hexamethyleneimine[q]	2	Cl	b_2 147–148	low	$C_9H_{16}ClNO$[r]	56.98	8.50	7.39	57.88	8.64	7.52
1,2,3,4-Tetrahydroquinoline	1	Cl	53–54[s]	69	$C_{11}H_{12}ClNO$	63.07	5.77	6.68	62.99	5.79	6.58
1,2,3,4-Tetrahydroquinoline	2	Cl	oil[t]	92	$C_{12}H_{14}ClNO$	64.43	6.31		64.57	6.27	
1,2,3,4-Tetrahydroquinoline	3	Cl	oil[u]	85	$C_{13}H_{16}ClNO$	65.68	6.78	5.89	65.47	6.72	6.01[v]
6-Methyl-1,2,3,4-tetrahydroquinoline	2	Cl	68[s]	90	$C_{13}H_{16}ClNO$	65.68	6.78		65.73	6.80	
6-Methyl-1,2,3,4-tetrahydroquinoline	2	Br	75–76[s]	79	$C_{13}H_{16}BrNO$	55.33	5.71	4.96	55.05	5.75	4.95[w]
6-Methoxy-1,2,3,4-tetrahydroquinoline	2	Cl	oil[x]	89	$C_{13}H_{16}ClNO_2$	61.54	6.35	5.52	61.51	6.52	5.54
1,2,3,4-Tetrahydrolepidine	1	Cl	67.5–68.5[s]	72	$C_{12}H_{14}ClNO$	64.43	6.31		64.27	6.12	
1,2,3,4-Tetrahydrolepidine	2	Cl	74[s]	74	$C_{13}H_{16}ClNO$	65.68	6.78		65.83	6.79	
1,2,3,4-Tetrahydrolepidine	2	Br	73–74[s]	76[h]	$C_{13}H_{16}BrNO$	55.33	5.71	4.96	55.44	5.66	4.92
1,2,3,4-Tetrahydrolepidine	3	Cl	oil[y]	75	$C_{14}H_{18}ClNO$	66.79	7.21		66.19	7.49	
1,2,3,4-Tetrahydroquinaldine	2	Cl	61–63[s]	77	$C_{13}H_{16}ClNO$	65.68	6.78	5.89	65.76	6.81	5.84
1,2,3,4-Tetrahydroisoquinoline	1	Cl	60–61[s]	69	$C_{11}H_{12}ClNO$	63.07	5.77		63.19	5.92	
1,2,3,4-Tetrahydroisoquinoline	2	Cl	B.p. 148–150/0.1	56	$C_{12}H_{14}ClNO$	64.43	6.31		64.52	6.50	

[a] Thanks go to Union Carbide Corp. for a sample of this material. [b] Reported m.p. 104–106°, Dr. J. A. Carbon, private communication. [c] Recrystallized from methanol. [d] Reported m.p. 189°, P. A. Barrett, *et al.*, *J. Chem. Soc.*, 2404 (1961). [e] Recrystallized from absolute ethanol. [f] The

hydrochloride was isolated from the reaction. [g] Recrystallized from aqueous ethanol. [h] Obtained from reaction of methyl iodide with the oily base from the hydrochloride. [i] Recrystallized from ethanol–ether. [j] Both the hydrochloride and free base were obtained from the reaction mixture in a total yield of 90%. Treatment of the hydrochloride with sodium bicarbonate and chloroform gave the same base. [k] Thanks go to Abbott Laboratories for a sample of this material. [l] Purified by chromatography on acid washed alumina. Decomposed on attempted distillation. See also Barrett, *et al.*, footnote *d*. [m] Thanks go to Dow Chemical Co. for a sample of this material. [n] A hygroscopic hydrochloride was obtained in 86% yield. All derivatives except the picrate, which could not be recrystallized, decomposed. The infrared spectrum of the oily base is consistent with the structure. [o] We would like to acknowledge helpful discussions with Dr. H. P. Schultz regarding the preparation of this compound. [p] Calcd.: Cl, 22.51. Found: Cl, 22.55. [q] Thanks go to the du Pont Co. for a sample of this material. [r] This material underwent considerable decomposition on distillation. [s] Recrystallized from low-boiling petroleum ether. [t] Purified by chromatography on acid washed alumina. [u] Purified by chromatography on alumina. [v] Calcd.: Cl, 14.96. Found: Cl, 14.72. [w] Calcd.: Br, 28.30. Found: Br, 28.20. [x] The reaction product was homogeneous on paper chromatography and not purified further. [y] 76% yield using 3-bromopropionyl bromide, 51% yield using 3-bromopropionyl chloride.

TABLE II

ALUMINA CHROMATOGRAPHY OF *N*-(3-CHLOROPROPIONYL)-AMIDES

Amide used	Product	M.p., °C.	Calcd., %			Found, %		
			C	H	N	C	H	N
1,4-Bis-(3-chloropropionyl)-1,2,3,4-tetrahydroquinoxaline	$C_{14}H_{14}N_2O_2$	172–174	69.40	5.82	11.57	69.08	5.85	11.60
1-(3-Chloropropionyl)-1,2,3,4-tetrahydroquinoline	$C_{12}H_{13}NO$	55–56[a]	76.97	7.00	7.48	77.08	7.19	7.46
1-(3-Chloropropionyl)-6-methyl-1,2,3,4-tetrahydroquinoline	$C_{13}H_{15}NO$	90–91	77.77	7.51	6.96	77.65	7.35	6.98
1-(3-Chloropropionyl)-6-methoxy-1,2,3,4-tetrahydroquinoline	$C_{13}H_{15}NO_2$	53–54	71.86	6.92	6.45	71.65	7.12	6.55
N-(3-Chloropropionyl)-phenothiazine	$C_{15}H_{11}NOS$	109–110	71.12	4.35		70.98	4.55	
1,4-Bis-(3-chloropropionyl)-piperazine		89–92[b]						

[a] B.p. 125° (0.5 mm.). [b] Reported m.p. 94–95° for 1,4-diacrylylpiperazine, Dr. J. A. Carbon, private communication. The infrared spectrum of this product was identical with an authentic spectrum. The material polymerized on standing.

TABLE III

LITHIUM ALUMINUM HYDRIDE REDUCTION OF AMIDES

Amide reduced	Product	M.p., °C.	Yield,[a] %	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1-(3-Chloropropionyl)-1,2,3,4-tetrahydroquinoline	$C_{12}H_{16}ClN \cdot HCl$	178–179[b]	68	58.55	6.96		58.85	7.12	
1-(Chloroacetyl)-1,2,3,4-tetrahydroquinoline	$C_{11}H_{14}ClN \cdot HCl$	134–135[c]	94			6.03			5.74
1-(3-Chloropropionyl)-6-methoxy-1,2,3,4-tetrahydroquinoline	$C_{13}H_{18}ClNO \cdot HCl$	193–194[d]	83	56.73	6.96	5.09	57.00	7.26	4.84
1-(Chloroacetyl)-1,2,3,4-tetrahydrolepidine	$C_{12}H_{16}ClN \cdot HCl$	150–151	79	58.55	6.96	5.69	58.83	6.72	5.74
1-(3-Chloropropionyl)-4-phenylpiperazine	$C_{13}H_{19}ClN_2 \cdot 2(C_6H_3N_3O_7)$[e]	161–163	88	43.08	3.62		43.41	3.62	

[a] Yields reported for the oily amine which was treated with ethanolic hydrochloric acid or picric acid for characterization. [b] Recrystallized from ethanol–ether. [c] Recrystallized from 2-butanone. [d] Recrystallized from ethanol–isopropyl ether. [e] The hydrochloride of the oily base was very hygroscopic but a dipicrate was obtained.

Surprisingly the closely related tetrahydroquinoxaline amide was inactive even at 500 mg./kg. Several of the 3-chloropropionyl amides also were found to exhibit little activity against Ca-755.[11]

Experimental[12]

General Method of Preparation of 1-(Haloacyl)-tetrahydroquinolines and Isoquinolines.—The amides of this type listed in Table I were prepared by adding 0.049 mole of haloacyl halide to 0.04 mole of the amine in 40 ml. of methylene chloride (or chloroform) at 5–10°. After coming to room temperature, the mixture was refluxed from 2 to 20 hr. Addition of a small amount of methanol and concentration *in vacuo* gave in most cases a solid. This solid was extracted in a Soxhlet for 24 hr. with low-boiling petroleum ether. Concentration of the extract gave the amide. Oils were purified directly.

General Method of Preparation of Other N-(3-Chloropropionyl) Amides.—To a solution of 1 mole of the amine in 600 ml. of dry chloroform was added, so as to maintain reflux, 1 mole of 3-chloropropionyl chloride. After the addition was complete, the mixture was refluxed until hydrogen chloride evolution had ceased. The reaction mixture then was filtered or (and) concentrated to give the amides in Table I.

Reaction of Diazomethane with 1,4-(Diacrylyl)-1,2,3,4-tetrahydroquinoxaline—An ethereal solution of 1.3 g. (0.0054 mole) of 1,4-(diacrylyl)-1,2,3,4-tetrahydroquinoxaline was treated with about 0.05 mole of diazomethane in ether. The mixture was kept at 0° for 24 hr. and at room temperature for 24 hr. Concentration gave 1.1 g. of solid, m.p. 156–159° (frothing), infrared: 3400 $cm.^{-1}$ (NH), 1640 $cm.^{-1}$ (C=O), 1565 $cm.^{-1}$ (C=N).

Anal. Calcd. for $C_{16}H_{18}N_6O_2$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.91; H, 5.63; N, 25.60.

Reduction of Amides.—A 50-ml. dried ethereal solution of 0.031 mole of amide was added dropwise with stirring to a 50-ml. ethereal solution of 1.4 g. (0.037 mole) of lithium aluminum hydride so as to maintain a gentle reflux. The mixture was then refluxed 4 hr. and water added. The ether layer was washed with water and dried ($MgSO_4$). Concentration *in vacuo* gave an oil which on treatment with 1.5 *N* ethanolic hydrogen chloride gave the hydrochloride (see Table III).

Acknowledgment.—We wish to acknowledge the technical assistance of Mr. H. Swarz and several helpful discussions with Dr. Leo Rane and with Dr. J. A. Carbon.

(11) Results supplied by the Cancer Chemotherapy National Service Center, U. S. Public Health Service.

(12) Analysis by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler & Strauss, Oxford, England. All melting points are uncorrected.