(see Fig. 4). Attempts to apply a two parameter distribution function[27] of the Schulz type to these data have not given particularly consistent results. The Lansing–Kraemer logarithmic distribution is considered a better representation of the data for Neoprene Type GN within the experimental errors of fractionations and molecular weight determinations.

Acknowledgment.—The authors gratefully acknowledge the helpfulness of preliminary experiments on the fractionation of neoprene carried out in this laboratory by Dr. S. L. Scott, now of the Service Department of the du Pont Company. Acknowledgments likewise are made to Dr. F. T. Wall and Dr. H. Mark for many helpful discussions during the course of this research and to Miss B. L. Price for her assistance in the osmotic pressure measurements.

Summary

Polychloroprene rubber, Neoprene Type GN, has been fractionated by partial precipitation from dilute solution in benzene and the fractions examined both osmotically and viscometrically in benzene solutions.

The molecular weight distribution curve for Neoprene Type GN based on osmotic pressure measurements shows a pronounced maximum at 100,000 but has a long extension to molecular weights of over one million, indicating the presence of branched or cross-linked material which is still soluble. The uniformity is somewhat less than that of sol natural rubber, while in shape the neoprene distribution curve resembles more closely that of a peptized natural rubber than fresh sol rubber.

Observed variations in the slopes of the π/c *vs.* c and the η_{sp}/c *vs.* c curves also indicate the presence in solution of complex, branched and/or cross-linked molecules.

Calibration of the intrinsic viscosity-molecular weight relationship by osmotic pressure measurements gave good agreement with the equation $[\eta] = KM^a$, where $K = 1.46 \times 10^{-4}$ and $a = 0.73$.

WILMINGTON, DELAWARE RECEIVED FEBRUARY 12, 1948

(27) G. V. Schulz, *Z. physik. Chem.*, **B43**, 25 (1939); R. F. Boyer, *Ind. Eng. Chem., Anal. Ed.*, **18**, 342 (1946); I. Jullander, *J. Polymer Sci.*, **2**, 329 (1947).

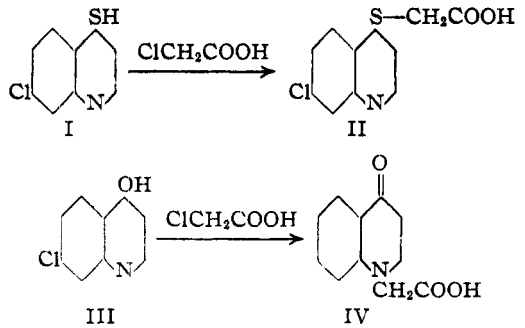
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Basic Esters and Amides of 4-Quinolylmercaptoacetic Acid Derivatives

BY ALEXANDER R. SURREY

The present investigation was undertaken to synthesize 4-quinolyloxy-, 4-quinolylamino- and 4-quinolylmercaptoacetic acid derivatives to make them available for pharmacological study.

It was observed that, in alcohol solution, 4,7-dichloroquinoline[1] reacts with thiourea to yield a thiouronium salt which on treatment with sodium carbonate gives 7-chloro-4-quinolinethiol (I) and a small amount of 7,7′-dichloro-4,4′-diquinolylsulfide. The thiol (I) reacts with chloroacetic acid



to give (7-chloro-4-quinolyl)-mercaptoacetic acid (II). The fact that compound II was also obtained by the reaction of 4,7-dichloroquinoline with mercaptoacetic acid indicates that the structure of II must be correct.

(1) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

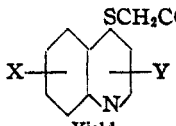
The behavior of the thiol, I, with chloroacetic acid is strikingly different from that of the corresponding 4-hydroxyquinoline, III. The reaction of III with chloroacetic acid yields only the 4-keto-1(4)-quinolineacetic acid IV. Similarly, when ethyl chloroacetate was allowed to react with 4-amino-7-chloroquinoline, ethyl 7-chloro-4-imino-1(4)-quinolineacetate (V) was obtained. The formation of IV and V is not unexpected when one considers the known behavior of similar compounds on treatment with alkyl iodide.[2] Hydrolysis of V with 5% sodium hydroxide solution gives the quinolone IV. Both V and the ethyl ester prepared from IV are high melting solids, insoluble in the usual organic solvents. A comparison of the ultraviolet absorption spectra of IV with the mercaptoacetic acid, II, is shown in Fig. 1.[3]

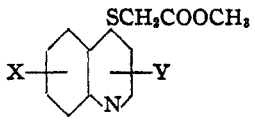
Inasmuch as the 4-amino- and 4-hydroxyquinolines did not give the desired intermediates, the present work was confined mainly to the 4-quinolylmercaptoacetic acid derivatives. The acids (Table I) were prepared from the corresponding 4-chloroquinoline by treatment with mercaptoacetic acid. The basic esters were prepared by ester interchange. Accordingly, the appropriate methyl ester (Table I) was refluxed in Skellysolve

(2) F. W. Bergstrom, *Chem. Rev.*, **35**, 133, 135, 177 (1944).

(3) The absorption spectra were determined in these laboratories under the direction of Dr. G. W. Ewing, present address Union College, Schenectady, N. Y.

TABLE I





X	Y	Yield, %	M. p., °C.	Nitrogen, % Calcd.	Found	M. p., °C.	Nitrogen, % Calcd.	Found
7-Cl	H	90	228–229	253.5[a]	254.1	99.5–100.5	5.23	5.13
5-Cl	H	67	221–222	5.52	5.49	102.5–103.5	5.23	5.02
6-OCH_3	H	50	236–237	5.62	5.65	82.5–83.5	5.31	5.35
H	H	63	233–234	6.39	6.28	192–193[b]	5.19	5.27
7-Cl	2-CH_3[c]	50	229–230	S, 11.96	12.08	105–106	4.97	4.97
7-Cl	3-CH_3[d]	63	186–188	5.23	5.18	77–78	4.97	4.97
5-Cl	3-CH_3[d]	61	189–190	5.23	5.12			
8-OCH_3	3-CH_3[e]	28	178–180	5.31	5.12	81.5–82	5.05	5.04
6-OCH_3	3-CH_3[f]	76	189–191	5.31	5.29	57–58	5.05	5.05
H	3-CH_3[f]	89	179–181	6.01	5.98	62–63	5.67	5.65
8-CH_3	3-CH_3[e]	78	170–172	5.67	5.67	55–56	5.36	5.34
8-OC_2H_5	3-CH_3[e]	52	198–199	5.05	4.97	81–82	4.81	4.88
6-Br	3-CH_3[f]	56	197–199	4.49	4.35	76–77	4.30	4.28
7-Cl	3-Br	58	202–204	4.21	4.03	78–79	5.05	5.05

[a] Neutral equivalent. [b] Hydrochloride. [c] For the corresponding 4-chloro compound see Steck, Hallock, Holland and Fletcher, THIS JOURNAL, **70**, 1012 (1948). [d] For the corresponding 4-chloro compound see Steck, Hallock and Holland, *ibid.*, **68**, 380 (1946). [e] Page 132. [f] Page 129.

E with an aminoalcohol or a primary tertiary amine, removing the methanol continuously as it formed to yield the basic ester (Table II) or basic amide (Table III). In one instance, the basic ester, diethylaminoethyl-(5-chloro-4-quinolyl)-mercaptoacetate, was prepared by heating the corresponding acid with 1-chloro-2-diethylaminoethane.[4]

Experimental[5]

7-Chloro-4-keto-1(4)-quinolineacetic Acid.—A mixture of 11 g. of 7-chloro-4-hydroxyquinoline, 5.8 g. of chloroacetic acid and 5.4 g. of sodium hydroxide in 32 cc. of water, was heated to dryness in a beaker over a free flame. The solid residue was dissolved in water, filtered hot with charcoal and the filtrate acidified with acetic acid. The separated solid was purified by dissolving in bicarbonate solution, filtering from any insoluble material, and acidifying the filtrate with acetic acid. The yield was 7 g. of a product that melted at 268–269°.

Anal. Calcd. for $C_{11}H_8ClNO_3$: neut. equiv., 237.6. Found: neut. equiv., 237.7.

The ethyl ester was prepared by refluxing 2 g. of the acid in 50 cc. of absolute ethanol containing 2.5 cc. of concentrated sulfuric acid for three hours. It was recrystallized from a large volume of ethanol, m. p. 194–195°.

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: N, 5.27. Found: N, 5.46.

Ethyl 7-Chloro-4-imino-1(4)-quinolineacetate.[6]—A mixture of 5.4 g. of 4-amino-7-chloroquinoline and 4 g. of ethyl chloroacetate in 11 cc. of pyridine was heated on the steam-bath for five minutes, cooled and diluted with water. The product which separated was recrystallized from 100 cc. of ethanol; yield, 3 g., m. p. 265–266° (immersed at 240°).

Anal. Calcd. for $C_{13}H_{13}ClN_2O_2$: N, 10.58. Found: N, 10.37.

Hydrolysis with 5% sodium hydroxide solution gave 7-chloro-4-keto-1 (4)-quinolineacetic acid.

(4) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

(5) All melting points are uncorrected.

(6) Prepared in this laboratory by Mr. Henry F. Hammer, present address Rensselaer Polytechnic Institute, Troy, New York.

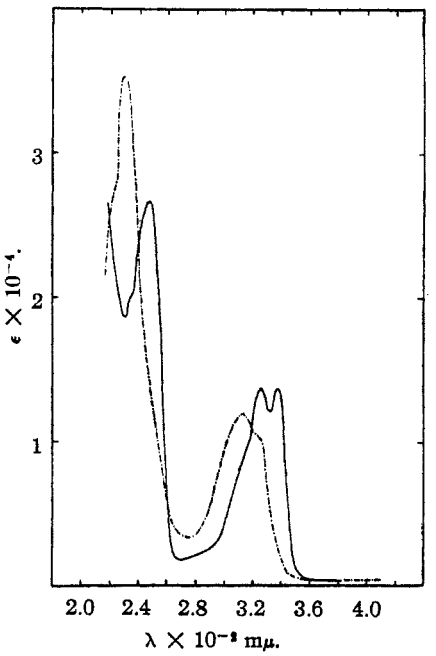


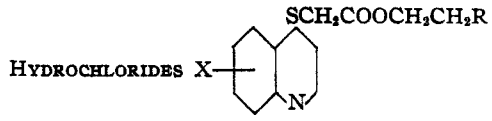
Fig. 1.—Ultraviolet absorption curves: —, compound IV; ·—·, compound II.

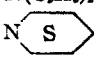
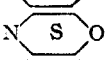
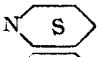
7-Chloro-4-quinolinethiol (I).—Thiourea (7.0 g.) was added to a warm solution of 19.8 g. of 4,7-dichloroquinoline in 200 cc. of absolute alcohol. After shaking for a few minutes the entire contents of the flask solidified. The white solid was filtered off, dissolved in water and the solution made alkaline with sodium carbonate. The yellow-orange solid which separated was filtered off and dissolved in dilute sodium hydroxide solution. A small amount of insoluble material was obtained which was recrystallized from pyridine, m. p. 166–167°. It analyzed for 7,7'-dichloro-4,4'-diquinolylsulfide.

Anal. Calcd. for $C_{18}H_{10}Cl_2N_2S$: S, 8.96. Found: S, 8.90.

The alkaline solution was acidified with acetic acid to

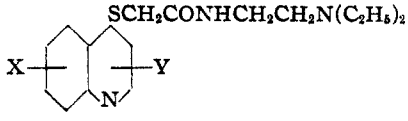
TABLE II



X	R	Recryst. solvent	Yield, %	M. p., °C.	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine[a] Calcd.	Chlorine[a] Found
H	$N(C_2H_5)_2$	Isopropanol	71	154–155	7.16[b]	6.97	18.16	18.18
5-Cl	$N(CH_3)_2$	Methanol–ethyl acetate	37	180–181	7.76	7.80	9.83	9.60
5-Cl	$N(C_2H_5)_2$	Ethanol	84	199–201	7.20	7.14	9.14	8.88
5-Cl		Ethanol	50	179–180	6.40[b]	6.69	16.23	15.90
5-Cl		Methanol–acetone	42	214–215	6.37[b]	6.40	16.15	15.81
6-OCH_3	$N(C_2H_5)_2$	Isopropanol	55	154–155	7.28	7.20	9.23	9.19
7-Cl	$N(CH_3)_2$	Ethanol	36	170–172	7.76	7.50	9.83	9.72
7-Cl	$N(C_2H_5)_2$	Ethanol	60	145–146	7.20	7.19	9.14	8.85
7-Cl		Ethanol	70	165–166	6.98	6.72	8.85	8.80
7-Cl		Methanol–ethyl acetate	21	199–201	6.37[b]	6.37	16.15	15.84

[a] Ionic chlorine. [b] Dihydrochloride.

TABLE III



X	Y	M. p., °C.	Nitrogen, %[a] Calcd.	Nitrogen, %[a] Found	M. p., °C.	Hydrochlorides Analyses, % Sulfur Calcd.	Sulfur Found	Chlorine[b] Calcd.	Chlorine[b] Found
7-Cl	H	98–99	11.95	12.24	130–131	N, 11.03	10.83	9.15	9.24
5-Cl	H	87–88	7.97	7.95	131–133.5	8.25	8.09	9.15	9.16
6-OCH_3	H	54–55	8.06	8.02	159–160	8.34	8.40	9.26	9.43
H	H	61–62	8.83	8.77	114–115	9.05	9.06	10.04	10.00
7-Cl	2-CH_3	108.5–109.5	7.66	7.65	127–128	7.96	7.85	N, 10.43	10.24
7-Cl	3-CH_3				162–163	7.96	7.77	8.83	8.59
8-OCH_3	3-CH_3	102.5–103.5	7.76	7.65	138–139	8.05	8.20	8.93	8.75
6-OCH_3	3-CH_3	78–79	7.76	7.72	137–138	8.05	8.09	8.93	8.68
H	3-CH_3				130–131	8.71	8.65	9.66	9.56
8-CH_3	3-CH_3	85–87	8.12	8.06	114–116	8.41	8.32	N, 11.01	10.82
8-OC_2H_5	3-CH_3	94–95	7.47	7.41	130–131	7.78	7.78	8.63	8.54
6-Br	3-CH_3				166–168	7.17	7.06	7.95	7.88
7-Cl	3-Br	130–131	9.75	9.72	165–168	6.85	6.92	N, 8.99	8.83

[a] Titration of basic nitrogen by the Toennies and Callan method (*J. Biol. Chem.*, 125, 259 (1938)). [b] Ionic chlorine.

give the yellow thiol which was recrystallized from acetic acid; yield, 12.5 g., m. p. 196–197°.

Anal. Calcd. for C_9H_5ClNS: N, 7.16. Found: N, 6.96.

7-Chloro-4-quinolylmercaptoacetic Acid. Procedure A.—A mixture of 7-chloro-4-quinolinethiol, chloroacetic acid and sodium hydroxide was treated in the same manner as for the 4-hydroxy compound above. The yield was almost quantitative. The acid was purified by solution in 10% sodium carbonate solution followed by precipitation with acetic acid.

Procedure B.—A pyridine solution of 19.8 g. of 4,7-dichloroquinoline and 11 g. of thioglycolic acid was refluxed for three hours, sodium hydroxide added and the pyridine removed by steam distillation. The alkaline solution was treated with acetic acid, the separated solid was heated on the steam-bath with ethanol, and further purified as above; yield 8.5 g. A mixed melting point determination with the acid prepared above showed no depression. Similarly, the methyl esters prepared from both acids were identical.

Procedure C.—The following method was used for the acids described in Table I. Three hundred grams of 4,7-dichloroquinoline, 147 g. of thioglycolic acid and 256 cc. of 35% sodium hydroxide solution in 1.7 liters of absolute ethanol was refluxed with stirring for one hour. The sodium salt of the acid which separated was filtered off, dissolved in water and purified as above. Where the sodium salt failed to separate, refluxing was continued for eight to sixteen hours, the alcohol removed by distillation and the residue dissolved in water and purified as above.

Methyl 7-Chloro-4-quinolylmercaptoacetate.—The methyl esters described in Table I were prepared by refluxing the acids in methanol containing concd. sulfuric acid. The above ester was also prepared from the acid chloride. Five grams of 7-chloro-4-quinolylmercaptoacetic acid and 3.4 g. of phosphorus pentachloride in 100 cc. of dry benzene was refluxed with stirring for one hour. After distilling off the solvent, the residue was refluxed for one hour with methanol. The residue, after removing most of the methanol, was dissolved in water and the solution treated with sodium carbonate solution. The methyl

ester which separated was filtered off and recrystallized from Skellysolve C; yield 2.5 g., m. p. 98–100°.

The **ethyl ester**, after recrystallization from Skellysolve B, melted at 60–61°.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: N, 4.97. Found: N, 4.82.

The **amide** was prepared from the methyl ester with alcoholic ammonia at room temperature. After recrystallization from acetic acid and then ethanol it melted at 213–214°.

Anal. Calcd. for $C_{11}H_9ClN_2OS$: N, 11.09. Found: N, 11.04.

α-(7-Chloro-4-quinolyl)-mercaptopropionic Acid.—The acid was prepared from ethyl α-bromopropionate and 7-chloroquinolinethiol (I) by refluxing in dilute sodium hydroxide solution; yield 83%. After recrystallization from ethanol, the acid melted at 202–204°.

Anal. Calcd. for $C_{13}H_{10}ClNO_2S$: N, 5.23; neut. equiv., 267.5. Found: N, 4.95; neut. equiv., 265.1.

The **methyl ester hydrochloride** was recrystallized from isopropanol, m. p. 167–168°.

Anal. Calcd. for $C_{14}H_{13}Cl_2NO_2S$: N, 4.40; Cl^-, 11.17. Found: N, 4.14; Cl^-, 10.84.

β-(7-Chloro-4-quinolyl)-mercaptopropionic Acid.—Prepared from β-chloropropionic acid and I; yield 52%, m. p. 212–214°.

Anal. Calcd. for $C_{13}H_{10}ClNO_2S$: N, 5.23; neut. equiv., 267.5. Found: N, 5.24; neut. equiv., 261.5.

The **methyl ester** after recrystallization from Skellysolve B, melted at 84.5–86°.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: N, 4.97. Found: N, 4.69.

Ethyl (5-Chloro-4-quinolyl)-mercaptoacetate.—Prepared from the corresponding acid, m. p., 40–41°, from Skellysolve A.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: N, 4.97. Found: N, 4.97.

The **amide**, recrystallized from ethanol, melted at 226–228°.

Anal. Calcd. for $C_{11}H_9ClN_2OS$: N, 11.09. Found: N, 11.06.

β-Diethylaminoethyl α-(7-Chloro-4-quinolyl)-mercaptopropionate Dihydrochloride.—The procedure described below is the general method used for the preparation of the basic esters described in Table II.

A mixture of one mole of methyl α-(7-chloro-4-quinolyl)-mercaptopropionate and four moles of diethylaminoethanol in Skellysolve E was refluxed with a water separator for about six to twelve hours or until no more methanol separated. The rate of reflux was maintained at such a rate that practically no Skellysolve E was collected along with the methanol. In most cases the theoretical amount of methanol was collected.

The Skellysolve was distilled under reduced pressure and the crude residue was dissolved in ether and washed thoroughly with water. After removing the ether by distillation the residue (60–95% yields) was dissolved in ten volumes of acetone, filtered with charcoal, and to the filtrate was added a slight excess of alcoholic hydrogen chloride. If necessary ether was added to precipitate the hydrochloride. The product was recrystallized from ethanol, yield 45%, m. p. 199–201°.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S \cdot 2HCl$: N, 6.37; Cl^-, 16.16. Found: N, 6.05; Cl^-, 15.92.

β-Diethylaminoethyl β-(7-chloro-4-quinolyl)-mercaptopropionate recrystallized from a mixture of isopropanol and acetone, m. p. 175–176.5°.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S \cdot 2HCl$: N, 6.37; Cl^-, 16.16. Found: N, 6.20; Cl^-, 15.94.

γ-Diethylaminopropyl 7-chloro-4-quinolylmercaptoacetate recrystallized from isopropanol, yield 60%, m. p. 157.5–158.5°.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S \cdot HCl$: N, 6.95; Cl^-, 8.81. Found: N, 6.87; Cl^-, 8.78.

β-Diethylaminoethyl (5-Chloro-4-quinolyl)-mercaptoacetate Hydrochloride.—To a hot suspension of 12.7 g. of 5-chloro-4-quinolylmercaptoacetic acid in 60 ml. of dry isopropanol was added 6.8 g. of 2-chloro-1-diethylaminoethane. After stirring for fifteen minutes a clear solution was obtained. After twenty minutes the contents of the flask solidified, crude yield, 16.5 g., m. p. 177–188°. The product was purified by several recrystallizations from ethanol.

N-2-Diethylaminoethyl 4-Quinolylacetamides (Table III).—The general procedure for the preparation of the basic amides is essentially the same as for the basic esters described above. The appropriate methyl ester (0.1 mole) was refluxed with 0.2 mole of N,N-diethylethylenediamine in 200 cc. of Skellysolve E for about eight hours or until no more methanol was collected. In most instances, a solid product was obtained after removal of the solvent under reduced pressure. These amides could be recrystallized from one of the Skellysolve fractions. The hydrochlorides were prepared in the usual manner.

Acknowledgment.—The author wishes to acknowledge the technical assistance of Miss Marcia Rukwid. The analyses reported were performed by the analytical staff of this Institute.

Summary

The reaction of 7-chloro-4-hydroxyquinoline or 4-amino-7-chloroquinoline with chloroacetic acid or ethyl chloroacetate results in the formation of 1-quinolineacetic acid derivatives. Under similar conditions, 7-chloro-4-quinolinethiol yields the corresponding 4-quinolylmercaptoacetic acid.

The preparation of several 4-quinolylmercaptoacetic and propionic acid derivatives is reported.

RENSSELAER, NEW YORK RECEIVED FEBRUARY 3, 1948