reactions it was not found that increasing the size of the alkyl substituent caused a noticeable diminishing of reactivity. This was true even when the substituent was as large as hexadecyl. Only low yields of the expected addition products were obtained using the procedure described by Bruson and Riener[3] for additions with ethyl or *n*-butyl substituted malonates. Furthermore, reactions under these conditions were slow.

Experimental

The alkylmalonic esters used in this study were prepared as described in an earlier paper.[10] The experiments described in the following paragraphs typify the different procedures used. Numerical data are given in Table I.

TABLE I

ADDITION OF ALKYLMALONIC DIETHYL ESTERS TO ACRYLONITRILE

Alkyl substituent	Method and % yield	B. p.[a] adduct, °C. (1 mm.)	$n^{25}D$ of adduct	Nitrogen, % Calcd.	Found
n-Butyl	A 87	133–134[b]	1.4413	5.19	5.16
n-Hexyl[c]	A 82	149–150	1.4436	4.70	4.61
n-Octyl[c]	B 90	163–165	1.4460	4.31	4.43
n-Decyl[c]	A 89	173–174	1.4482	3.96	3.86
n-Dodecyl[c]	B 92	182–183	1.4491	3.67	3.50
n-Tetradecyl[c]	D 86	189–190	1.4511	3.41	3.28
Cetyl[c]	C 89	M. p. 45°	Solid[d]	3.19	3.07

[a] Boiling points are uncorrected; determined in an alembic still at a distillation rate of 2–3 drops per second. A 6-inch indented column was used to prevent superheating. [b] Bruson and Riener give the boiling point of this adduct as 145–150° (1 mm.). [c] These adducts are new compounds. [d] Colorless needles.

Addition of Ethyl *n*-Butylmalonate to Acrylonitrile

Method A (in Alcohol).—A solution of 0.1 g. of metallic sodium in 20 ml. of absolute ethanol was prepared. To it was added 21.6 g. (0.1 mole) of ethyl *n*-butylmalonate and the solution was mechanically stirred while 8 g. of acrylonitrile was added slowly. The heat of the reaction caused the temperature to rise rapidly and it was maintained at about 70° by adjusting the rate of addition of the acrylonitrile. The reaction mixture was allowed to stand for about two hours after which it was acidified to litmus with glacial acetic acid and the solvent was evaporated off under reduced pressure. The residual liquid was taken up in ether, washed and dried over sodium sulfate. The addition product was distilled under reduced pressure after removal of the ether. No low-boiling fraction was obtained.

Addition of Ethyl *n*-Dodecylmalonate to Acrylonitrile

Method B (in Benzene).—A solution of ethyl *n*-dodecylmalonate (0.1 mole) in dry benzene was prepared and to it was added 0.05 g. of sodium metal. Using the usual apparatus, acrylonitrile (0.11 mole) was slowly added to the yellow solution. The temperature of the reaction mixture was maintained at 30–40° during the reaction by means of a cooling bath and no solid acrylonitrile polymer was formed under these conditions. The reaction mixture was processed and the reaction product distilled under reduced pressure.

Addition of Ethyl Cetylmalonate to Acrylonitrile

Method C (in Benzene).—Ethyl cetylmalonate (30 g.) was dissolved in dry benzene and to the solution was added 0.1 g. of sodium methoxide dissolved in 1 ml. of ethanol. Then acrylonitrile (5 g.) was added slowly to the solution at such a rate that the reaction temperature did not rise above 70°. A small amount of yellow solid (acrylonitrile polymer) settled out of the solution. An additional three grams of acrylonitrile was added to replace that lost in polymer formation. After acidification and concentration of the filtrate there was obtained a solid product melting at 45°. Recrystallization from 80% ethanol did not alter the melting point of the crystals.

Addition of Ethyl *n*-Tetradecylmalonate to Acrylonitrile

Method D (No Solvent).—A solution of 0.05 g. of sodium ethoxide in 0.5 ml. of absolute ethanol was prepared and to it was added ethyl *n*-tetradecylmalonate (0.05 mole), followed by acrylonitrile (0.055 mole). The reaction temperature was maintained at 60–70° by adjusting the rate of addition of the acrylonitrile. The reaction mixture was processed as before, the product isolated by ether extraction and distilled under reduced pressure.

Summary

The addition reactions of a series of alkylmalonic esters with acrylonitrile and the physical properties of the adducts have been described. The influence of various solvents and bases on the reaction have been discussed on the basis of the present theory of addition of active hydrogen systems to acrylonitrile.

MINNEAPOLIS 13, MINN. RECEIVED NOVEMBER 1, 1948

(10) Floyd and Miller, THIS JOURNAL, **69**, 2354 (1947).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some 6-Quinolyl Sulfides and Sulfones

BY HENRY GILMAN AND GORDON C. GAINER[1a]

As a result of the high antistreptococcal activity of 4,4′-diaminodiphenyl sulfone[1b] and the inhibitory effect of this compound on experimental tuberculosis in animals,[2] together with the indicated antimalarial activity of certain of its derivatives,[3] a series of quinoline analogs of this compound has been prepared.

It is known that the dinitro and diaminodiphenyl sulfides and sulfones have therapeutic effects similar to that of sulfanilamide,[1,4,5] but are generally more toxic, [6,7] and since the introduction of some heterocycles in sulfanilamide adds desirable features, it was thought that certain sulfides and sulfones of quinoline might have therapeutic value.

(1a) Present address: Westinghouse Research Laboratories, East Pittsburgh, Pa.

(1b) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **1**, 1331 (1937).

(2) Rist, Block, and Hamon, *Ann. Inst. Pasteur*, **64**, 203 (1940).

(3) (a) Heymann and Fieser, THIS JOURNAL, **67**, 1979 (1945); (b) Heymann and Heidelberger, *ibid.*, **67**, 1986 (1945).

(4) Fourneau, J. and Mme. J. Trefouel, Nitti and Bovet, *Bull. acad. med.*, **118**, 210 (1937); *Compt. rend.*, **204**, 1763 (1937).

(5) Bauer and Rosenthal, *U. S. Pub. Health Rpts.*, **53**, 40 (1938).

(6) Welch, *J. Pediatrics*, II, no. 2, 159 (1937).

(7) Raiziss, Clemence, Severae and Moetsch, THIS JOURNAL, **61**, 2763 (1939).

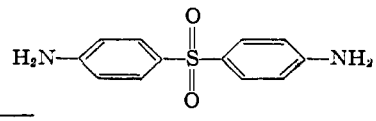
Certain modifications of 4,4′-diaminodiphenyl sulfone have been made in an attempt to obtain drugs which are more suitable for clinical application. Bambas[8] states that the toxic character of 4,4′-diaminodiphenyl sulfone precludes its use as a drug in clinical tuberculosis. In the hope of reducing the toxicity and yet retaining the antistreptococcal and antituberculous activity of the compound, Bambas prepared a number of analogs of the compound in which one or both of the phenyl rings were replaced by heterocyclic rings. The only quinoline derivatives prepared in his study were 5-amino-8-quinolyl *p*-acetaminophenyl sulfone and the corresponding deacetylated compound. As a result of these studies, Bambas concluded that only those compounds which have at least one benzene nucleus with nitrogen in the para-position to the sulfur are effective.

Certain other sulfides and sulfones of the benzene ring of quinoline have been described. Surrey and Lindwall[9] prepared 8,8′-dinitro-5,5′-diquinolyl and 5,5′-dinitro-8,8′-diquinolyl sulfides, and the sulfone of the latter, for therapeutic testing.

Winter and Reinhart[10] record the preparation of certain 8-quinolyl phenyl sulfides and sulfones for testing as antistreptococcal agents. In their work, 5-nitro-8-quinolyl phenyl sulfide and the corresponding amino compound were synthesized. In addition, 5-nitro-8-quinolyl *p*-nitrophenyl sulfide and sulfone were prepared.

In connection with certain studies in these laboratories on experimental avian malaria and antituberculous agents, an examination of the syntheses of some sulfur-substituted heterocycles has been made. The preparation of 8-amino-6-quinolyl methyl sulfone[11a] and γ-(6-methoxy-8-quinolylamino)-propyl β-diethylaminoethyl sulfone[11b] have been reported. Recently, a sulfur analog of the well known Plasmochin type, 8-(γ-diethylaminopropylamino)-6-quinolyl methyl sulfide, has been described.[12] Certain long-chained alkyl, substituted 6-quinolyl sulfides have also been prepared.[13]

It was thought desirable to synthesize a series of compounds in which one of the benzene nuclei of 4,4′-diaminodiphenyl sulfone was replaced by a 6-quinolyl or substituted 6-quinolyl group, at the same time retaining the nitrogens in the equivalent para-position to the sulfur as found in 4,4′-diaminodiphenyl sulfone, thus:



(8) Bambas, THIS JOURNAL, **67**, 668 (1945).

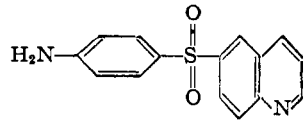
(9) Surrey and Lindwall, *ibid.*, **62**, 173 (1940).

(10) Winter and Reinhart, *ibid.*, **62**, 3508 (1940).

(11) (a) Gilman and Lindblad, *ibid.*, **68**, 982 (1946); (b) Gilman and Fullhart, *ibid.*, **67**, 1585 (1945).

(12) Gilman, Benkeser, Gainer, Lindblad, Marshall, Massie, Myers and Tolman, *ibid.*, **68**, 1577 (1946).

(13) S. P. Massie, Doctoral Dissertation, Iowa State College (1946).



In extending the investigation on the type of compound represented by 6-quinolyl *p*-aminophenyl sulfide and sulfone, there have been prepared certain 5-nitro-6-quinolyl and 5-nitro-8-amino-6-quinolyl *p*-aminophenyl sulfides and sulfones, and derivatives of these. In all of these, except 5-nitro-6-quinolyl *p*-chlorophenyl sulfide, a nitro, amino or acetamido group occupied a position para to the sulfur linkage, the latter, in turn, always being para to the nitrogen contained and included in the quinoline nucleus. This latter requirement was fulfilled by the exclusive use of the 6-quinolyl or substituted 6-quinolyl group. This arrangement of the nitrogen and sulfur groups thus paralleled the relative positions of these groups in the antistreptococcal compounds of the benzene series.

The 6-quinolyl *p*-substituted phenyl sulfides and sulfones were prepared either directly or indirectly by use of the Skraup reaction. For example, 6-quinolyl *p*-nitrophenyl sulfide and sulfone were prepared in good yield by application of the arsenic oxide modification of the Skraup synthesis to 4-nitro-4′-amino- (or preferably 4′-acetamido-) diphenyl sulfide and sulfone, respectively. The corresponding 6-quinolyl *p*-aminophenyl sulfide and sulfone were conveniently obtained by catalytic reduction of the parent nitro compounds.

The series of 5-nitro-6-quinolyl *p*-substituted phenyl sulfides and sulfones was prepared by interaction of the sodium salt of the desired thiophenol or sulfinic acid with the labile chlorine atom of 5-nitro-6-chloroquinoline. The 5-amino-6-quinolyl compounds were prepared by catalytic reduction of the parent nitro compounds.

For the preparation of the 5-nitro-8-amino-(or acetamido)-6-quinolyl *p*-substituted phenyl sulfones, the labile chlorine atom of 5-nitro-6-chloro-8-amino(or acetamido)- quinoline was reacted with the sodium salt of *p*-acetamidobenzenesulfinic acid.

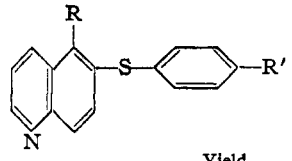
It also seemed desirable to prepare a few compounds which incorporate the *p*-aminophenyl group with an aliphatic side-chain containing the sulfone group. One of the compounds prepared, γ-(*p*-aminophenoxy)-propyl β-chloroethyl sulfone, had marked vesicant action.

Continuing the studies initiated in these laboratories on the preparation of antimalarials with sulfur-containing side-chains,[11,12,13] γ-(6-methoxy-8-quinolylamino)-propyl mercaptan was prepared by the condensation of 6-methoxy-8-aminoquinoline with γ-chloropropyl mercaptan.

Acknowledgment.—The authors are grateful to Parke, Davis and Company for arranging for the tests, the results of which will be reported

TABLE I

6-QUINOLYL SULFIDES



R	R'	Prepared from	Yield, %	M. p., °C.	Nitrogen, % Calcd.	Found
H	NO_2	4-Nitro-4'-aminodiphenyl sulfide[a]	55	168.5–169.5	9.93	9.87[i]
H	$NH_2 \cdot 2HCl$	6-Quinolyl *p*-nitrophenyl sulfide[b,c]	78	217–218	8.63	8.84
NO_2	NH_2	$C_9H_5N_2O_2Cl$[d] + sodium *p*-aminothiophenolate[e]	90	137–138	14.15	14.16
NH_2	$NH_2 \cdot 3HCl$	5-Nitro-6-quinolyl *p*-aminophenyl sulfide[b,c]	88	261–262	11.15	11.30
NO_2	$NHCOCH_3$	5-Nitro-6-quinolyl *p*-aminophenyl sulfide[f]	94	173–174	12.42	12.57
		$C_9H_5N_2O_2Cl$[d] + sodium *p*-acetamidothiophenolate[g]	80			
NO_2	Cl	$C_9H_5N_2O_2Cl$[d] + *p*-chlorothiophenol[h]	88	115–116	8.84	8.98

[a] The amino compound[14] (0.1 mole) was stirred to a paste with 0.40 mole of glycerol and 0.074 mole of arsenic pentoxide. Conc. sulfuric acid (21 g.) was added with stirring while temperature was maintained below 130°; temperature was then kept at 130–135° for an hour, and the mixture further refluxed for six hours. The hot mixture was then poured over ice, neutralized with 40% sodium hydroxide, and filtered. The residue was dried, charcoaled, and recrystallized from acetone–95% ethanol. [b] The nitro compound (0.05 mole) in absolute ethanol was shaken for one hour with Raney nickel at 95–100°, under 3 atmospheres of hydrogen; the catalyst was then filtered off. [c] The filtered solution from the reduction was evaporated to a syrup, freed from water by repeated azeotropic evaporation with benzene–absolute ethanol, and treated with ethanolic hydrogen chloride. The precipitated hydrochloride was recrystallized from absolute ethanol. [d] = 5-Nitro-6-chloroquinoline. [e] The thiophenol (0.026 mole) was added to an equivalent amount of sodium ethoxide in ethanol to give the sodium salt; 0.024 mole of the quinoline in absolute ethanol was added; the mixture was refluxed for half an hour, then diluted with water and filtered, and the residue washed with 95% ethanol and dried. [f] The amino compound was acetylated by refluxing two hours in acetic anhydride–acetic acid and then pouring into water. After filtration, washing with 95% ethanol, and drying, the compound was purified by recrystallization from 95% ethanol and drying *in vacuo*. [g] The procedure was the same as in footnote *e* except that 0.08 mole of the thiophenol and the quinoline were used and except that sodium hydroxide and 95% ethanol were used in the reaction in place of the sodium ethoxide and absolute ethanol. [h] Prepared exactly as in footnote *f* except that 0.05 mole each of the thiophenol and of the quinoline were used. Recrystallization from 95% ethanol did not raise the m. p. of the crude material. [i] Sulfur: calcd. 11.32; found 11.20.

elsewhere. They also wish to thank John Morton and William Meikle for assistance.

Experimental

γ-(*p*-Nitrophenoxy)-propyl β-Hydroxyethyl Sulfone.—To a stirred solution of 70 g. (0.275 mole) of crude γ-(*p*-nitrophenoxy)-propyl β-hydroxyethyl sulfide[11b] in glacial acetic acid was added 96 g. (0.84 mole) 30% hydrogen peroxide, temperature being maintained below 60°. The mixture was heated on a steam cone until reaction began, then removed from the cone and allowed to stand until refluxing ceased, and, finally, refluxed with stirring for two hours, cooled, and poured over an excess of chopped ice, with stirring. Filtration and drying gave a quantitative yield of crude material melting at 88–95°. The solid was purified by refluxing with stirring for five hours in 2 liters of 2 *N* sulfuric acid, so as to hydrolyze any acetate ester. The mixture was cooled and filtered, and the residue dried to give 70 g. (85%) of brown solid, melting with sintering at 85–95°. Treatment with charcoal and recrystallization from 95% ethanol gave pale yellow crystals melting at 103–104°. *Anal.* Calcd. for $C_{11}H_{15}O_6NS$: N, 4.84. Found: N, 5.01.

γ-(*p*-Nitrophenoxy)-propyl β-Acetoxyethyl Sulfone.—This compound, originally isolated as a by-product from the above oxidation, was also prepared by heating 2.9 g. (0.01 mole) γ-(*p*-nitrophenoxy)-propyl β-hydroxyethyl sulfone in 10 g. (0.1 mole) acetic anhydride at 125° for one-half hour. The mixture was cooled and poured over an excess of chopped ice. The solid so obtained was washed twice with sodium bicarbonate solution, then filtered and dried *in vacuo* to give a quantitative yield of product which softened at 78° and melted at 81–82°. Recrystallization from 95% ethanol raised the melting point to 85–86°.

Anal. Calcd. for $C_{13}H_{17}O_7NS$: N, 4.23. Found: N, 4.21.

6-Quinolyl *p*-Nitrophenyl Sulfide.—By a procedure similar to that used for the preparation of the sulfone, 50 g. (0.20 mole) of 4-nitro-4'-aminodiphenyl sulfide[14] was converted to 54 g. (95%) of crude 6-quinolyl *p*-nitrophenyl sulfide, melting at 150–155°. After charcoaling and crystallizing from an acetone–95% ethanol mixture, there was obtained 31 g. (55%) of product melting at 167–168°. The material for analysis melted at 168.5–169.5°.

Anal. Calcd. for $C_{15}H_{10}O_2N_2S$: N, 9.93; S, 11.32. Found: N, 9.87; S, 11.20.

***p*-Aminothiophenol.**—This compound was prepared by refinement of the method of Lantz.[15] A mixture of 480 g. (2 moles) of sodium sulfide nonahydrate dissolved in two liters of water and 128 g. (0.81 mole) of *p*-chloronitrobenzene was refluxed for eight hours. The small amount of orange colored oil which had formed on cooling was removed by ether extraction and discarded. The aqueous layer was saturated with sodium chloride and 240 g. (4 moles) of glacial acetic acid was added and the liberated oil extracted several times with ether. Subsequent to drying over sodium sulfate, evaporative distillation of the ether, and vacuum distillation, 70 g. (69%) of product distilling at 143–146° (17 mm.), and melting at 43–45° was obtained (lit. 46°).[16]

***p*-Substituted Phenyl 6-Quinolyl Sulfides and Sulfones.**—Tables I and II list a series of *p*-substituted phenyl 6-quinolyl and *p*-substituted phenyl-substituted 6-quinolyl sulfides and sulfones. These were prepared in essential accordance with the directions given for the synthesis of *p*-aminophenyl 5-nitro-6-quinolyl sulfide and the corresponding *p*-acetamidophenyl sulfone. The sodium salt of the appropriate substituted thiophenol or substituted sulfinic acid was treated with the labile chlorine atom of the required 5-nitro-6-chloroquinoline to yield the desired product.

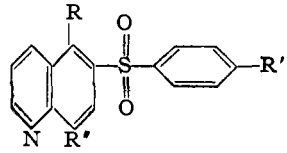
(14) Lantz, French Patent 715,359; English Patent 376,961; U. S. Patent 1,965,776; see also ref. 7.

(15) Lantz, French Patent 714,682 (1931) [*Chem. Zentr.*, **103**, 1829 (1932)].

(16) Zincke and Jorg, *Ber.*, **42**, 3366 (1909).

TABLE II

6-QUINOLYL SULFONES



R	R	R′	Prepared from	Yield, %	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
H	NO_2	H	4-Nitro-4′-aminodiphenyl sulfone[a]	67	181–182	...	...	10.18	10.24
H	NH_2	H	6-Quinolyl *p*-nitrophenyl sulfone[b]	88	178–179	9.85	10.05	...	...
NO_2	$NHCOCH_3$	H	$C_8H_8NO_3SNa$[c] + $C_9H_5N_2O_2Cl$[d]	100[h]	247–248	11.32	11.36	8.64	8.74
NO_2	NH_2	H	5-Nitro-6-quinolyl *p*-acetamidophenyl sulfone[e]	100[h]	258–259	...	...	9.73	9.76
NO_2	$NHCOCH_3$	$NHCOCH_3$	$C_8H_8NO_3SNa$[c] + 5-nitro-6-chloro-8-acetamidoquinoline[f]	92	313-314	13.10	13.30	...	...
NO_2	NH_2	NH_2	5-Nitro-8-acetamido-6-quinolyl *p*-acetamido sulfone[g]	91	247–247.5	16.20	16.40	...	...
NO_2	$NHCOCH_3$	NH_2	$C_8H_8NO_3SNa$[c] + 5-nitro-6-chloro-8-aminoquinoline[g]	95	261.5–262.5	...	...	8.30	8.42

[a] See Gabel and Grinberg, *J. Applied Chem.* (*U. S. S. R.*), **12**, 1481 (1939) [*C. A.*, **34**, 6244 (1940)]. The amino compound (0.1 mole) was stirred to a paste with 0.40 mole glycerol and 0.074 mole arsenic pentoxide. Conc. sulfuric acid (21 g.) was added with stirring while temperature was maintained below 130°; temperature was then kept at 130–135° for an hour, and the mixture further refluxed for six hours. The hot mixture was then poured over ice, neutralized with 40% sodium hydroxide and filtered. The residue was dried, charcoaled, and recrystallized from acetone–95% ethanol. [b] The nitro compound (0.03 mole) in absolute ethanol was shaken for one hour with Raney nickel at 95–100°, under 3 atmospheres of hydrogen; the catalyst was then filtered off, and the filtrate concentrated to yield crystalline product. [c] = Sodium *p*-acetamido-benzene sulfinate. [d] = 5-Nitro-6-chloroquinoline. The mixture of the sodium salt (0.11 mole) and the quinoline (0.10 mole) was refluxed for three and one-half hours in a mixture of ethylene glycol and methyl cellosolve, diluted with water, and filtered, and the residue washed with 95% ethanol and dried. The product was recrystallized to constant melting point from ethylene glycol–methyl cellosolve. [e] These hydrolyses were accomplished by 15-minute refluxing in hydrochloric acid (250 ml., 6 *N* for 0.043 mole of 5-nitro-6-quinolyl *p*-acetamidophenyl sulfone; 150 ml., 8 *N* for 0.017 mole of 5-nitro-8-acetamido-6-quinolyl *p*-acetamidophenyl sulfone), followed by neutralization of the solution, filtration, and drying of the residue. [f] The mixture of the sodium salt (0.044 mole) and the quinoline (0.04 mole) was refluxed for three and one-half hours in a mixture of ethylene glycol and methyl cellosolve, diluted with water and filtered, and the residue washed with 95% ethanol and dried, and recrystallized for analysis from methyl cellosolve. [g] The mixture of the sodium salt (0.036 mole) and the quinoline (0.033 mole) was refluxed for three and one-half hours in a mixture of ethylene glycol and methyl cellosolve, diluted with water, and filtered, and the residue washed with 95% ethanol and dried, and recrystallized for analysis from methyl cellosolve. [h] Crude.

γ-(*p*-Aminophenoxy)-propyl β-Hydroxyethyl Sulfone.[17]—In a steam-jacketed pressure flask heated to 95–100°, containing a solution of 135 ml. of acetone and 15 ml. of absolute ethanol, 9.7 g. (0.034 mole) of γ-(*p*-nitrophenoxy)-propyl β-hydroxyethyl sulfone (m. p. 103–104°) was hydrogenated over Raney nickel as catalyst under three atmospheres pressure of hydrogen. After shaking for one hour the Raney nickel was filtered off and the water-white filtrate evaporated to dryness *in vacuo*. Filtration and drying gave 8.7 g. (92%) of white crystalline product which melted at 131–132°. Upon recrystallization to constant melting point from 95% ethanol, the compound melted at 133.5–134°.

Anal. Calcd. for $C_{11}H_{17}O_4NS$: N, 5.40. Found: N, 5.53

γ-(*p*-Aminophenoxy)-propyl β-Chloroethyl Sulfone Hydrochloride.—With cooling and vigorous shaking, 11 g. (0.043 mole) of finely powdered γ-(*p*-aminophenoxy)-propyl β-hydroxyethyl sulfone was dusted into 100 g. (0.93 mole) of pure thionyl chloride held at 0° by means of an ice–salt-bath. The mixture was then gently warmed with continued shaking beginning with a cold water-bath. The solution so obtained was refluxed gently for one hour and the bulk of the excess thionyl chloride was then distilled off under vacuum. The last of the thionyl chloride was removed by the dropwise addition of absolute ethanol to the ice-cold liquid residue. The semi-solid hydrochloride so obtained was then dissolved in warm absolute ethanol, charcoaled, filtered and allowed to crystallize. Filtering and drying *in vacuo* gave 10.5 g. (70%) of pale yellow crystals of the hydrochloride which melted at 175–176°. The product for analysis melted at 179–180°.

Anal. Calcd. for $C_{11}H_{17}O_3NCl_2S$: N, 4.46; Cl, 22.44. Found: N, 4.47; Cl, 22.48.

γ-(6-Methoxy-8-quinolylamino)-propyl Mercaptan Hydrochloride.—In an atmosphere of nitrogen a mixture of 17.5 g. (0.1 mole) of 6-methoxy-8-aminoquinoline and 12.6 g. (0.115 mole) of γ-chloropropyl mercaptan[18] was heated by an oil-bath at 100° for three-fourths hour. The temperature was then slowly raised to 130° over a period of one and one-half hours, at the end of which time the temperature of the oil-bath was held at 135° for fifteen hours. After cooling, 100 ml. of water and 5 ml. of concentrated hydrochloric acid were added to effect solution. An excess of 20% sodium hydroxide was added, and the mixture exhaustively extracted with ether. After acidification of the alkaline solution, the aqueous solution was made alkaline with ammonium hydroxide and the liberated mercaptan exhaustively extracted with ether. Subsequent to drying, evaporative distillation of the ether and vacuum distillation, 8 g. (32%) of a pale yellow viscous oil boiling at 174–178° (0.5 mm.) was collected. This was dissolved in anhydrous ether, and the solution treated with methanolic hydrogen chloride and filtered. The bright orange crystalline product melted at 168–170°.

(17) SN 11,005 (See Wiselogle, "A Survey of Antimalarial Drugs 1941–1945," Vol. 2, J. W. Edwards, Ann Arbor, Mich., 1946, p. 622).

(18) Sjorberg, *Ber.*, **74**, 64 (1941).

When recrystallized to constant melting point from absolute methanol, the compound sintered at 171° and melted at 172–173.5°.

Anal. Calcd. for $C_{13}H_{17}ON_2ClS$: N, 9.83; S, 11.22. Found: N, 9.83; 9.82; S, 11.25; 11.20; 11.10

Summary

6-Quinolyl *p*-nitrophenyl sulfide and sulfone have been prepared by application of the Skraup synthesis.

By the interaction of the sodium salts of appropriate substituted thiophenols and *p*-acetamidobenzenesulfinic acid with the labile chlorine atom of 5-nitro-6-chloroquinoline or 5-nitro-6-chloro-8-amino-(or acetamido-)-quinoline, the synthesis of a series of substituted 6-quinolyl sulfides and sulfones has been effected.

Some *p*-aminophenyl derivatives containing the sulfone group in an alkyl "side-chain" have been prepared.

In connection with studies on experimental avian malaria, γ-(6-methoxy-8-quinolylamino)-propyl mercaptan hydrochloride has been synthesized.

AMES, IOWA RECEIVED AUGUST 10, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Formula of Zygadenine

BY F. W. HEYL AND M. E. HERR

A number of years ago one of us isolated from Death Camas leaves a crystalline alkaloid[1] which belongs in the veratrine group.[2] A year or more later a further quantity of this alkaloid, which we called zygadenine, was prepared in this Laboratory. It was subjected to both acid and alkaline hydrolysis but neither carbohydrate nor angelic acid could be detected and the basic fraction failed to crystallize.

More recently the work of Jacobs and others has brought an orderly system to the consideration of this class of alkaloids.[3]

With this highly detailed development in the chemistry of the veratrine alkaloids it did not appear difficult to restudy zygadenine and more clearly fit it into the systematized knowledge in this field. The data in the experimental part indicate that zygadenine has the formula $C_{27}H_{43}O_7N$. It belongs in the series of alkamines which Jacobs and Craig have tabulated as follows: veratramine, $C_{27}H_{39}O_2N$; rubijervine and isorubijervine, $C_{27}H_{43}O_3N$; jervine, $C_{27}H_{39}O_3N$; an unnamed alkaloid, $C_{27}H_{41}O_4N$, from veratrum viride[4]; cevine and isogermine, $C_{27}H_{43}O_8N$; and protoverine, $C_{27}H_{43}O_9N$.

Zygadenine does not form a nitroso compound and is a tertiary base. It appears to be a new alkamine closely related to cevine and germine but containing one less oxygen. The specific rotation of zygadenine differs from those of cevine (−17.52°) and of germine (+5.0°) but it closely approaches that of isogermine (−46.5°).[5] The latter melts above 245° while zygadenine melts at 201–204°.

(1) F. W. Heyl, F. E. Hepner and S. K. Loy, THIS JOURNAL, **35**, 258 (1913).

(2) P. H. Mitchell and G. Smith, *Am. J. Physiol.*, **28**, 318 (1911).

(3) F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945); W. A. Jacobs and L. C. Craig, *ibid.*, **155**, 565 (1944); **160**, 564 (1945); **170**, 635 (1947); W. Poethke, *Arch. Pharm.*, **275**, 571 (1937); **276**, 179 (1938).

(4) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **160**, 555 (1945); **149**, 451 (1943).

(5) L. C. Craig and W. A. Jacobs, *ibid.*, **148**, 60 (1943).

Experimental[6]

Preparation of Crude Alkaloidal Fractions.—Thirteen and six-tenths kilograms of the dried Death Camas leaves were exhausted with 95% alcohol and the percolate was concentrated to about 6 l. The concentrate was diluted with about 12 l. of water in which 60 g. of tartaric acid had been dissolved. The precipitated resin was removed, the clear solution rendered alkaline with ammonia and the crude alkaloids extracted with chloroform.

The alkaloids were re-extracted with 5% tartaric acid solution and reprecipitated with ammonia. The precipitate "A" (43.6 g.) was filtered, washed with water and dried *in vacuo*. An additional 22.9 g. was extracted from the ammoniacal filtrate with chloroform (fraction "B") so that the total yield of crude alkaloid was equivalent to 0.49% of the dried leaves.

Properties of Fraction "A" above.—When 1.0 g. was saponified with sodium hydroxide in methanol by the method described below, there resulted upon steam distillation of the "volatile acids" 3 thirty-minute distillates which required, respectively, 2.94, 2.4 and 1.9 ml. of 0.05 *N* alkali, from which it may be concluded that fraction "A" contained not more than 20% of esterified alkaloid. In fact this fraction was largely zygadenine and was the source of its preparation in the previous publication.[1]

Zygadenine.—The crude alkaloid "B" served to prepare zygadenine. It was dissolved in boiling alcohol and 17.5 g. of the alcohol addition product crystallized. Fractional crystallization from alcohol yielded four top fractions weighing, respectively, 7.0 g., 6.7 g., 2.1 g., and 0.6 g. The first fraction upon analysis showed the presence of 11.4% alcohol of crystallization. It was dried at 100° *in vacuo* and crystallized from benzene when $[\alpha]^{24}D$ −45° in chloroform. It melted at 201–204°.

Anal. Calcd. for $C_{27}H_{43}O_7N$: C, 65.7; H, 8.8; N, 2.84. Found: C, 65.9, 66.1, 66.1; H, 8.50, 8.75, 8.76; N, 3.17, 2.97, 2.92.

The first three fractions were combined, freed from alcohol and systematically fractionated from benzene. A top fraction weighing 9.88 g. was again crystallized from benzene. It weighed 4.23 g. and upon analysis showed no differences from those reported above. Despite repeated crystallization the carbon content remained on the high side of that required by the steroid formula.

The alkaloid contained neither methoxyl nor N-CH_3 groups. It did not precipitate with digitonin and failed to give any coloration with a 90% solution of trichloroacetic acid.

(6) We wish to acknowledge with thanks the coöperation of the Upjohn microanalytical group.