been screened for pharmacological activity. One of those examined, 2-mercaptomethyl-5,6-dihydroimidazo[ij]quinoline (VI) was active toward dextran edema; however, the remaining seven compounds displayed no pharmacological activity.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Commercial intermediates were used without further purification. Yields correspond to the amount of pure product obtained.

Starting materials. The 8-aminoquinoline (m.p. 63–64°) was produced by an iron and acetic acid reduction of the 8-nitro compound[22] or in 67% yield from oxine[23] employing a reaction ratio of 1:2:10 of oxine, ammonium sulfite, and ammonia. When the amount of sodium in the sodium-alcohol reduction of 8-aminoquinoline[4] was increased to 14–15 g.-atoms per mole of 8-aminoquinoline, the yield rose to 84% of pure 8-amino-1,2,3,4-tetrahydroquinoline, b.p. 145° at 2 mm. Isonicotinyl chloride was obtained from the acid with thionyl chloride in 88% yield, b.p. 95–96° at 25 mm, by an adaptation of Koo's method.[24]

Directions for the methods used in the preparation of the dihydroimidazo[ij]quinolines and related compounds are to be found as footnotes to the appropriate table.

8-Nitro-1-acetyl-1,2,3,4-tetrahydroquinoline. A solution of 1-acetyltetrahydroquinoline (6.7 g. 0.0382 mole) in 10 ml. of acetic anhydride was cooled and treated cautiously with a solution of 3.6 g. (0.04 mole) of 70% nitric acid in 10 ml. of acetic anhydride. After 0.5 hr. in an ice bath, the red mixture was allowed to stand at room temperature overnight (12 hr.). The solution was poured onto ice. The oil which separated was extracted with ether and the ethereal solution was washed with dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent yielded 7.3 g. (89%) of the product as a red oil, which, on acid hydrolysis afforded the known 8-nitro-1,2,3,4-tetrahydroquinoline, m.p.: 82–84° (lit.,[25] m.p. 82–83°).

8-Amino-1,2-dihydroquinoline (LII). A slurry of 6.5 g. (0.174 mole) of lithium aluminum hydride in 150 ml. of absolute diethyl ether was heated to boiling with stirring. To the slurry was added 5.0 g. (0.0347 mole) of 8-aminoquinoline (Eastman) dissolved in 50 ml. of absolute diethyl ether. The mixture was refluxed for 24 hr. during which time the initially blood-red slurry became lighter and a yellow solid remained. The slurry was cooled to 0° and water was added cautiously with stirring under a nitrogen atmosphere until hydrolysis was complete. The mixture was filtered, the filtrate dried over magnesium sulfate, and the solvent evaporated and the residue distilled. The green-yellow oil boiled at 157–160° (6 mm.).

Anal. Calcd. for: $C_9H_{10}N_2$: C, 73.94; H, 6.91; N, 19.17. Found: C, 73.10; H, 6.71; N, 18.50–18.63.

A picrate formed as golden-brown needles which melted at 204–205° and showed no depression in melting point when admixed with authentic 8-aminoquinoline picrate. In another experiment, an orange picrate formed which melted at 192–194° and showed a depression of 20° when admixed with 8-aminoquinoline picrate. When the orange picrate was recrystallized from 95% ethanol, however, golden-brown needles resulted which melted at 200–201° and proved to be 8-aminoquinoline picrate by a mixture melting point.

Condensation of certain acids with 8-amino-1,2-dihydroquinoline. A. Formic acid. A solution of 1.1 g. (0.0075 mole) of 8-amino-1,2-dihydroquinoline in 25 ml. of 85% formic acid was refluxed overnight (13–17 hr.). The orange solution was cooled and made alkaline with dilute ammonium hydroxide, whereupon a silvery solid separated which was filtered, washed with water, and recrystallized from methanol to yield colorless needles which melted at 148.0–148.5°. A mixture melting point with authentic 8-formamidoquinoline (XLII) showed no depression, and an analysis and ultraviolet spectrum confirmed the 8-formamidoquinoline structure.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.77; H, 4.65; N, 16.27. Found: C, 69.90; H, 4.96; N, 16.78.

B. Acetic acid. Reaction with acetic acid afforded only 8-acetamidotetrahydroquinoline, m.p. 100–101° (lit.,[21] m.p. 102–103°).

Acknowledgment. The authors wish to express their thanks to Dr. C. H. Tilford, Dr. G. L. Krueger, and the Wm. S. Merrell Company for their interest, advice, and financial assistance during the course of this work. Thanks are due also to Dr. V. B. Fish of Lehigh University who performed the analyses.

BETHLEHEM, PA.

(22) R. P. Dikshoorn, *Rec. Trav. Chim.*, **48**, 147 (1929).

(23) N. W. Woroshtzow and J. M. Kogan, *Ber.*, **65**, 142 (1932).

(24) J. Koo, *J. Am. Chem. Soc.*, **75**, 720 (1953).

(25) R. Stoermer, *Ber.*, **31**, 2523 (1898).

[CONTRIBUTION FROM THE DIVISION OF SCIENCES, LOUISIANA STATE UNIVERSITY IN NEW ORLEANS]

Preparation of 5,6-Dihydro-1,3-thiazines and 2-Thiazolines from Mercaptoalcohols and Nitriles[1]

ALBERT I. MEYERS

Received January 18, 1960

Treatment of certain mercaptoalcohols with nitriles in cold concentrated sulfuric acid results in a one-step nuclear synthesis of dihydro-1,3-thiazines and 2-thiazolines. This ring closure has been found to be applicable to a wide variety of nitriles.

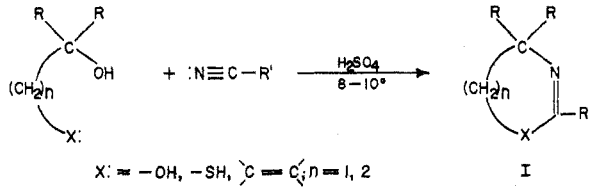
Earlier methods of synthesis of dihydro-1,3-thiazines and 2-thiazolines have been extensively reviewed by Elderfield[2] and Kuhn and Drawert[3]

(1) Presented before the 15th Annual Southwest Regional meeting of the American Chemical Society, Baton Rouge, La., December 3–5, 1959.

(2) R. C. Elderfield and E. E. Harris, *Heterocyclic Compounds*, Vol. 6, R. C. Elderfield, ed., J. Wiley and Sons, Inc., New York, 1957, p. 604.

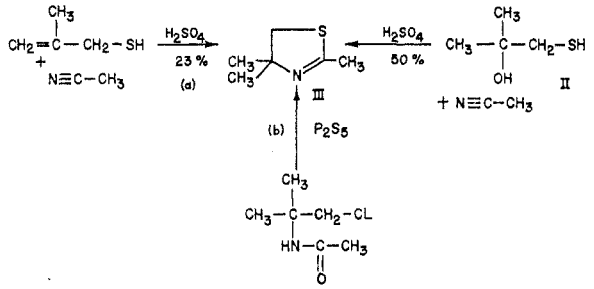
(3) R. Kuhn and F. Drawert, *Ann.*, **590**, 55 (1954).

respectively. More recently there have appeared several reports on new methods of obtaining these heterocyclics from the treatment of diacylated aminoalcohols with phosphorus pentasulfide[4] and the reaction of nitriles with methallyl mercaptan in sulfuric acid.[5] The latter method is part of a new



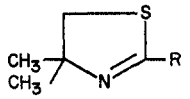
and general synthetic route to *N*-heterocycles of the type, I. Heterocyclic bases which have been prepared by this method and reported to date include 5,6-dihydro-1,3-oxazines,[6] 1-pyrrolines, 5,6-dihydropyridines, and 2-thiazolines.[5] This type of ring closure is presently considered as an extension of the Ritter *N*-alkylamide[7] synthesis which is brought about by the sulfuric acid-catalyzed reaction of nitriles and tertiary alcohols or olefins.

2-Thiazolines. Addition of 2-methyl-2-hydroxypropanethiol (II) to a cold solution of acetonitrile in concentrated sulfuric acid leads to the formation of 2,4,4-trimethyl-2-thiazoline (III) in about 50% yield. Comparison of the physical properties of this product with that prepared from (a) methallyl mercaptan and acetonitrile and (b) *N*-(2-chloro-*tert*-butyl)acetamide and phosphorus pentasulfide[8] revealed the product to be the same *via* all three routes.



The use of the mercaptoalcohol, rather than the unsaturated mercaptan, in the preparation of the 2-thiazolines possesses two distinct advantages. First, the yield of the 2-thiazoline was considerably higher (Table I) when the mercaptoalcohol was employed. This is attributed to the fact that the alcohol does not polymerize as readily as the methallyl mercaptan in concentrated sulfuric acid. This contrast in behavior has been previously observed[5] in the preparation of other *N*-heterocycles by this method. The second advantage in using the mercaptoalcohol lies in the fact that only an equimolar ratio of nitrile to mercaptoalcohol is required whereas a twofold excess of the methallyl mercaptan was necessary to yield the 2-thiazoline in approximately half the amount. The excess methallyl mercaptan was originally employed in an attempt to overcome the extensive polymerization that it had undergone in the acid medium.

TABLE I

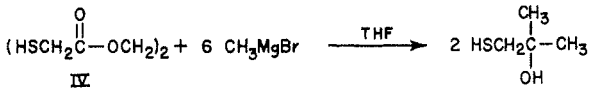


2-SUBSTITUTED 4,4-DIMETHYL-2-THIAZOLINES

Nitrile	R	% Yield of 2-Thiazoline from: Methallyl Mercaptan[a]	% Yield of 2-Thiazoline from: 2-Methyl-2-hydroxypropanethiol
Acetonitrile	Methyl	23	50
Acrylonitrile	Vinyl	22	47
Benzonitrile	Phenyl	24	51
p-Aminobenzonitrile	*p*-Aminophenyl	....	55

[a] See ref. 5.

The mercaptoalcohol, previously unreported, was prepared in 40% yield by the action of glycol dimercaptoacetate (IV) with methylmagnesium bromide in tetrahydrofuran. This reaction proceeded poorly in diethyl ether, due to the insolubility of the magnesium salt of the mercaptoester.



5,6-Dihydro-1,3-thiazines. When 3-methyl-3-hydroxy-*n*-butanethiol was added to a previously cooled solution of a nitrile in concentrated sulfuric acid, there was obtained a 2-substituted-4,4-dimethyl-5,6-dihydro-1,3-thiazine (VI) in 41–53% yield. A considerable quantity of polymeric material accompanied the formation of the product. Eight 5,6-dihydro-1,3-thiazines were prepared in this manner and their physical constants appear in Table II. This dihydro-1,3-thiazine synthesis further illustrates the scope of this nuclear nitrogen heterocyclic synthesis from nitriles. The formation of the thiazine ring is currently considered to occur in a manner completely analogous to the 2-thiazoline synthesis. As previously pointed out,[5] the primary adduct, V, which is similar to that which forms in Ritter *N*-alkylamide synthesis, is capable of ring closure if an electron-rich group is suitably situated elsewhere in the molecule.

(4) V. G. Bach and M. Zahn, *J. Prakt. Chem.*, **8**, 68 (1959).

(5) A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).

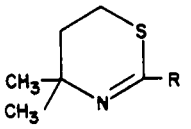
(6) E. J. Tillmans and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

(7) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045, 4048 (1948).

(8) S. H. Babock and R. Adams, *J. Am. Chem. Soc.*, **59**, 2260 (1937).

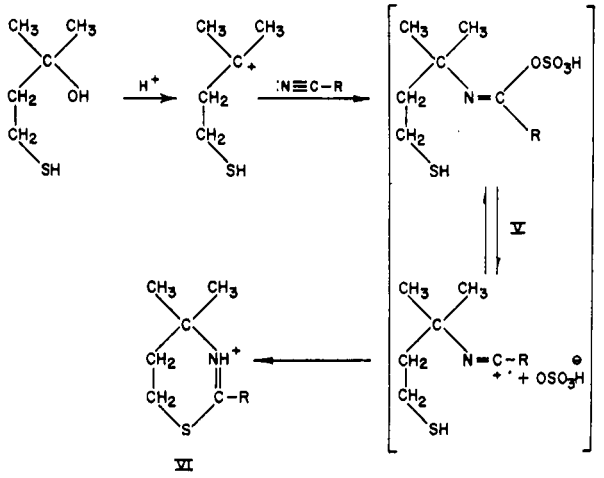
TABLE II

2-SUBSTITUTED 4,4-DIMETHYL-5,6-DIHYDRO-1,3-THIAZINES



No.	R	B.P.°, mm.	n_D^{30}	Yield, %	Formula	C Calcd.	C Found	H Calcd.	H Found	Picrate[a] M.P.,°
1	H	63–64/11	1.5109	42	$C_6H_{11}NS$	55.81	55.91	8.54	8.48	198–201
2	CH_3	53–54/1.5	1.5051	41	$C_7H_{13}NS$	58.71	58.39	9.01	8.93	176–177
3	C_2H_5	62–63/1.3	1.4943	46	$C_8H_{15}NS$	61.14	61.07	9.55	9.42	145–146
4	CH_2=CH	60–62/1.3	1.5273	51	$C_8H_{13}NS$	61.93	62.01	8.38	8.29	144–146
5	C_6H_5	119–121/1.3	1.5810	48	$C_{12}H_{15}NS$	70.22	70.31	7.33	7.30	141–142
6	p-$CH_3C_6H_4$	136–137/1.3	1.5750	50	$C_{13}H_{17}NS$	71.23	71.03	7.76	7.66	173–174
7	o-$CH_3C_6H_4$	130–131/1.5	1.5656	45	$C_{13}H_{17}NS$	71.24	70.89	7.70	7.44	166–167
8	p-$NH_2C_6H_4$	95–96[b]	...	53	$C_{12}H_{16}N_2S$	65.46	65.46	7.27	7.19	133–134

[a] Recrystallized from ethanol. [b] Melting point, recrystallized twice from 50% aqueous ethanol.

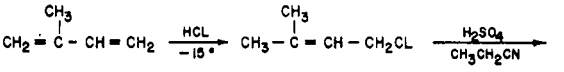


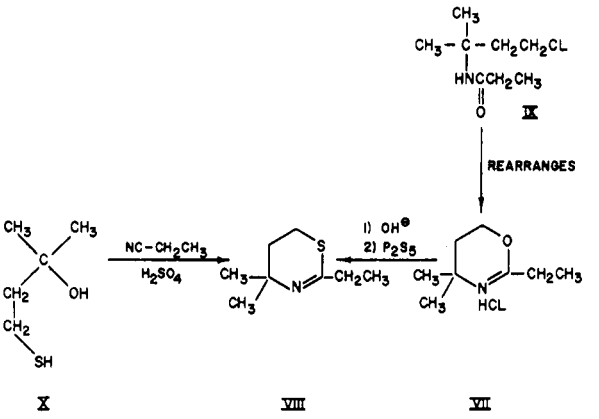
VI

Thus far, the hydroxyl, thiol, and alkene groups have served as nucleophilic centers which have participated in ring closure with the *nitrilium* ion (R—N=C—R). The question of the existence of the *nitrilium* species in this reaction is still at hand. The possibility also exists that the ring closure may occur by the nucleophilic attack of the thiol group on the *nitrilium* sulfate (R—N=C(OSO$_3$H)R) with subsequent displacement of the bisulfate ion. These possibilities are currently under consideration and an attempt to establish the mechanism of this step in the ring closure is in progress. One fact that lends support to the over-all proposed mechanism of this reaction is that on the basis of the dihydro-1,3-oxazine synthesis,[6] all the subsequent heterocyclic systems prepared by this method were predicted before actually being performed.

The structure of the 5,6-dihydro-1,3-thiazines were proven by an alternative method of synthesis. By heating 2-ethyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine (VII) with phosphorus pentasulfide for two hours at 150°, 2-ethyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine (VIII) was obtained. The oxazine was prepared by treating 4-chloro-2-methyl-2-butene[9] with propionitrile according to the method of Ritter and Lusskin.[10] The oxazine, rather than the expected *N*-(3-chloro-1-methyl-butyl-2) propionamide (IX) was isolated directly.[11]

These workers found that in some cases the *N*-(chloroalkyl)amides rearranged directly without treatment with base. Comparison of the physical properties of the thiazine prepared from propionitrile and the mercaptoalcohol with those of the thiazine prepared directly[12] from the oxazine showed both products to be identical.





X VIII VII

The infrared spectra of the 2-alkyl-5,6-dihydro-1,3-thiazines revealed a strong band in the 6.11–6.15μ region which is attributed to the cyclic unconjugated C=N link on the basis of a previous

(9) (a) W. J. Jones and H. W. T. Chorley, *J. Chem. Soc.*, 1946, 832; (b) A. J. Ultee, *Rec. trav. chim.*, 68, 125 (1949).

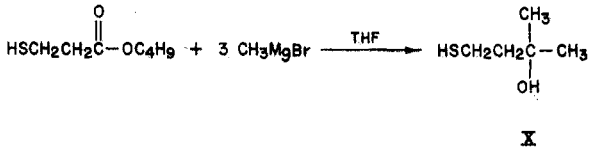
(10) J. J. Ritter and R. M. Lusskin, *J. Am. Chem. Soc.*, 72, 5577 (1950).

(11) See footnote in reference 5.

(12) S. Gabriel and T. Posner, *Ber.*, 27, 3519 (1894).

investigation.[13] The spectra of the 2-aryl derivatives and the 2-vinyl derivatives showed strong bands in 6.20–6.30μ region. A comparison of the C=N absorption of these dihydro-1,3-thiazines with the C=N absorption of dihydro-1,3-oxazines will be reported in a subsequent communication.

The synthesis of 3-hydroxy-3-methyl-*n*-butanethiol (X) in 63% yield was accomplished by treating *n*-butyl 3-mercaptopropionate with an excess of methylmagnesium bromide in tetrahydrofuran. As mentioned earlier, the use of tetrahydrofuran was necessary due to the insolubility of the magnesium salt of the mercaptoester in diethyl ether.



X

EXPERIMENTAL[14,15]

Glycol dimercaptoacetate (b.p. 129–130° at 5 mm., n_D^{25} = 1.5150) and *β-mercaptopropionic acid* (m.p. 18–19°) were kindly supplied by Evans Chemetics, New York City, N. Y.

2-Hydroxy-2-methylpropanethiol (II). Into a suspension of 91.0 g. (3.72 g.-atoms) of magnesium in 600 ml. of freshly distilled tetrahydrofuran[16] was passed *via* a sulfuric acid drying trap, sufficient methyl bromide to react completely with all the magnesium. The methyl bromide was introduced just above the surface of the suspension at a rate which produced a mild reflux. The completion of the methylmagnesium bromide took approximately 9 hr. Sixty-five grams (0.31 mole) of glycol dimercaptoacetate in 100 ml. of tetrahydrofuran was added to the refluxing Grignard solution in a dropwise manner and soon thereafter the external heating was discontinued due to the exothermic reaction which followed. The addition of the ester took 3.5 hr. and when addition was complete, the mixture was refluxed for an additional 3 hr., after which the condenser on the reaction flask was replaced by a simple distilling head and the solvent removed at reduced pressure. The dark slurry residue was then treated with 1.5 l. of saturated ammonium chloride solution and allowed to stand overnight at room temperature. The resulting two-layer system was separated into an organic and an aqueous phase. The latter was extracted several times with ether and the organic phase and the ethereal extracts were combined and dried over magnesium sulfate. Distillation of the residue, after the ether had been removed at atmospheric pressure, yielded 26.3 g. (40%) of a colorless liquid, b.p. 61–63° (15 mm.), n_D^{30} = 1.4710.

Anal. Calcd. for $C_4H_{10}OS$: C, 45.28; H, 9.43; S, 30.19. Found: C, 45.14; H, 9.36; S, 29.98.

2-(p-Aminophenyl)-4,4-dimethyl-2-thiazoline. This procedure can be considered as typical of all the 2-thiazolines prepared by this method. The physical constants of the other 2-thiazolines were reported in a previous paper.[5]

To a solution of 3.5 g. (0.03 mole) of *p*-aminobenzonitrile in 25 ml. of concd. sulfuric acid, previously cooled to 3°, was added with stirring 2.1 g. (0.02 mole) of 2-hydroxy-2-methylpropanethiol over a period of 30 min. The reaction mixture, which was golden yellow, was stirred at 3–5° for an additional hour after which it was poured on 300 g. of chipped ice. The cold aqueous acid solution was then extracted with chloroform until the chloroform layer was colorless. After passing the aqueous solution through filter paper (fluted) to remove the excess chloroform, it was carefully neutralized with 30% sodium hydroxide. The heterocyclic base appeared as a crude brown solid which was collected in a Buchner funnel and then washed several times with hot water to remove any unchanged nitrile. Recrystallization from aqueous ethanol yielded 2.3 g. (55%) of a very light yellow crystalline material, m.p. 162–164°. The picrate derivative melted at 91–93°.

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.07; H, 6.79; N, 13.59. Found: C, 63.88; H, 6.90; N, 13.41.

Structure proof of 2-thiazolines. The sequence of reactions which led to the confirmation of the structure of the 2-thiazolines has already been described in a previous publication.[5]

n-Butyl 3-mercaptopropionate. β-Mercaptopropionic acid (102 g., 0.96 mole), *n*-butyl alcohol (216 g., 3.0 moles), 400 ml. of benzene, and 3 ml. of concd. sulfuric acid were heated in a flask equipped with a motor stirrer and an azeotrope trap. After 8 hr., 25.5 ml. of water had been removed and the resulting solution was washed with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution, and again with 100 ml. of water. After drying over magnesium sulfate, the benzene and excess butanol were removed initially at atmospheric pressure and finally at reduced pressure. The residue was distilled *in vacuo* through a 12-inch glass-helices packed column and 146 g. (93.5%) of a colorless oil was obtained; b.p. 102.5–103.0° (11 mm.), n_D^{25} = 1.4539.

Anal. Calcd. for $C_7H_{14}O_2S$: C, 51.85; H, 8.64. Found: C, 52.10; H, 8.56.

3-Hydroxy-3-methyl-n-butanethiol (X). This compound was prepared utilizing the same procedure as described for 2-hydroxy-2-methylpropanethiol. Upon distillation, this reaction yielded 62.5 g. (63%) of a colorless oil, b.p. 52.0–53.5° (1.5 mm.), n_D^{20} = 1.4750.

Anal. Calcd. for $C_5H_{12}OS$: C, 50.00; H, 10.00; S, 26.66. Found: C, 49.94; H, 9.93; S, 26.33.

2-Substituted 4,4-dimethyl-5,6-dihydro-1,3-thiazines. A general procedure is described for the preparation of the dihydro-1,3-thiazines and the physical constants for these compounds are listed in Table II.

To a cold solution of 0.025 mole of nitrile in 25 ml. of concd. sulfuric acid, was added dropwise, with efficient stirring, 0.020 mole of 3-hydroxy-3-methyl-*n*-butanethiol. The temperature of the reaction during the addition was kept below 10° by means of external cooling. The addition of the mercaptan derivative usually required 20–30 min., after which stirring continued at 0–5° for an hour. The resulting pale yellow solution was then poured on 300–400 g. of chipped ice and set aside for several hours in a refrigerator. The aqueous acid solution was then freed of the always present gummy polymers by extraction with chloroform. The excess chloroform remaining in the aqueous layer was removed by filtration through fluted filter paper. Subsequent cautious neutralization of the acidic solution with 30% sodium hydroxide resulted in the appearance of the dihydro-1,3-thiazine. If the product was an oil, it was taken up in ether, dried over anhydrous potassium carbonate and distilled. If the product was a solid, it was collected in a Buchner funnel and then recrystallized from aqueous ethanol.

The picrate derivatives were formed by dissolving 0.2 g. of the heterocyclic base in ethanol and adding to it an equal volume of saturated ethanolic picric acid. The derivative usually formed immediately, otherwise heating the reactants to boiling and storage in a refrigerator overnight caused

(13) A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959).

(14) All melting points and boiling points are uncorrected.

(15) Microanalyses were performed by Alfred Bernhardt, Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany.

(16) The tetrahydrofuran (Matheson Coleman and Bell) was purified by allowing it to stand over sodium wire for 2 days and then, after filtering into a flask containing 100 g. of lithium aluminum hydride, distilled through a 24-inch column containing glass helices as packing material; b.p. 65.5–66.0°.

precipitation to occur. The picrates were recrystallized once from ethanol, dried in air, and the melting points determined.

Structure proof of the 5,6-dihydro-1,3-thiazines. (a) *4-Chloro-2-methyl-2-butene.* The method of Ultee[9b] was employed to prepare this compound; b.p. 50–52° (107 mm.); n_D^{30} = 1.4431 (reported[9b]: b.p. 51.5–52° (100 mm.) n_D^{20} = 1.4450).

(b) *2-Ethyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine* (VII). To a previously cooled solution of 2.75 g. (0.05 mole) of propionitrile in 20 ml. of coned. sulfuric acid was added slowly with efficient stirring 5.21 g. (0.05 mole) of 4-chloro-2-methyl-2-butene. The temperature of the mixture was kept below 10° during the addition. When the addition was completed, the deep yellow solution was allowed to warm up to room temperature and stirred for 3 hr. after which it was poured onto 200 g. of chipped ice. The aqueous solution was partially neutralized to *p*H 5.5 (Beckman Zeromatic *p*H meter) and no *N*-alkylamide (VIII) appeared. The solution was then further neutralized to *p*H 8.7 and extracted four times with 50-ml. portions of ether. After drying the ethereal extracts with anhydrous potassium carbonate overnight, the ether was removed on a steam bath and the residue distilled. There was obtained 4.23 g. (59%) of a colorless liquid possessing a strong ammoniacal odor; b.p. 52–53° (4 mm.); n_D^{30} = 1.4740.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.11; H, 10.62; N, 9.93. Found: C, 67.99; H, 10.55; N, 9.91.

(c) *2-Ethyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine* (VIII). An intimate mixture of 4.0 g. of 2-ethyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine (VI) and 10.0 g. of phosphorus pentasulfide was heated at 125° for 2 hr. in an oil bath (Hood!). When the very dark mixture cooled to room temperature, 50 ml. of 10% sodium hydroxide was added and the suspension agitated until no further odor of hydrogen sulfide could be detected. The oil, which had appeared at this point, was separated from the aqueous layer and after several ether extractions of the aqueous layer, the oil and the extracts were combined and dried over anhydrous potassium carbonate. Distillation of the residual oil, after removal of the ether, yielded 3.2 g. (71%) of a colorless compound whose physical properties were identical to those of compound 3 (Table II).

Acknowledgment. The author is grateful to the Frederick Gardner Cottrell Fund of the Research Corporation and to the National Institutes of Health, U. S. Public Health Service (DGMS-6248) for funds granted to support this study. Gratitude is also expressed to R. T. O'Connor of the Southern Regional Laboratory, United States Department of Agriculture, for providing infrared data.

NEW ORLEANS 22, LA.

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

Synthesis of Diaryloxazoles[1-3]

DUANE L. ALDOUS, J. L. RIEBSOMER, AND RAYMOND N. CASTLE

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Nine new oxazoles have been prepared and methods have been devised for introducing reactive side chains into 4,5-diphenyloxazole and 2,4-diphenyloxazole.

In recent years considerable interest has developed in oxazoles and oxazole quaternary salts. Hayes, *et al.*[4,5] synthesized a considerable number of 2,5-diaryloxazoles after it was discovered that 2-phenyl-5-(4-biphenylyl)oxazole was an effective scintillation solute. In 1956 Ott, Hayes, and Kerr[6] reported the synthesis of series of oxazole quaternary ammonium salts after it had been shown that certain compounds of this type possessed an extraordinary ability to lower the body temperature of animals.[7]

In this study several oxazoles and derivatives have been prepared in the hope that compounds with interesting physiological properties would be found.

The general approach to the synthesis of these oxazoles was suggested by the work of Davidson, Weiss, and Jelling[8] and by Dornow and Eichholz.[9] An aryl ketone (I) was converted to the α-bromoketone (II) which was allowed to react with the sodium salt of an acid to produce the ester (III). Ring closure to form the oxazole (IV) was then effected on the ester by refluxing with ammonium acetate in a solution of acetic acid.

In Table I is presented a series of esters of type III which were prepared by this method in which (I) was propiophenone. Table II lists a series of oxazoles (type IV) which were prepared from the

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