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).

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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

Received December 30, 1959

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

(1) This communication is based on work done under the auspices of the Los Alamos Scientific Laboratory and the Atomic Energy Commission.

(2) The authors are grateful to the Department of Chemistry, New Mexico Highlands University, Weiler and Strauss of Oxford, England, and to Dr. S. Yamada of the Tokyo Research Laboratory of Tanabe Seiyaku Co., Ltd., Tokyo, Japan, for carbon, hydrogen, and nitrogen analyses.

(3) Presented before the Division of Medicinal Chemistry of the American Chemical Society, April, 1960, Cleveland, Ohio.

(4) F. N. Hayes, L. C. King, and D. E. Peterson, *J. Am. Chem. Soc.*, **74**, 1106 (1952).

(5) F. N. Hayes, B. S. Rogers, and D. G. Ott, *J. Am. Chem. Soc.*, **77**, 1850 (1955).

(6) D. G. Ott, F. N. Hayes, and V. N. Kerr, *J. Am. Chem. Soc.*, **78**, 1941 (1956).

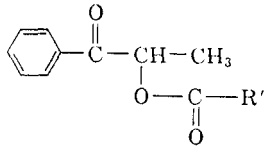
(7) C. C. Lushbaugh, F. N. Hayes, W. H. Langham, D. G. Scott, and P. C. Sanders, *J. Pharm. Exptl. Therap.*, **116**, 366 (1956).

(8) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 328 (1937).

(9) A. Dornow and H. Eichholz, *Ber.*, **86**, 384 (1953).

TABLE I

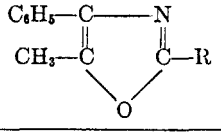
ESTERS OF α-HYDROXYPROPIOPHENONE



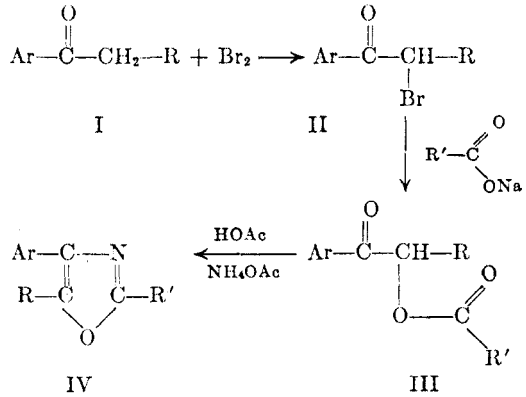
R′	M.P.°	Yield, %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Phenyl	109–110	69	Ethyl acetate	$C_{16}H_{14}O_3$	76.20	75.70	5.60	5.67		
α-Naphthyl	104.5–105.5	83	Ethyl acetate	$C_{20}H_{16}O_3$	78.90	79.10	5.30	5.56		
β-Naphthyl	105–107	67	Ethyl acetate	$C_{20}H_{16}O_3$	78.94	79.29	5.30	5.44		
2-Quinolyl	121–122	55	Ethyl acetate	$C_{20}H_{15}NO_3$	74.74	74.80	4.95	5.04	4.62	4.95
6-Quinolyl	120–121	62	95% Ethanol	$C_{19}H_{15}NO_3$	74.70	74.30	4.95	5.09	4.62	4.53
4-Pyridyl	112–113	23	95% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.65	5.13	5.36	5.49	5.58
3-Pyridyl	84.5–85.5	trace	50% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.28	5.13	5.30	5.49	5.37
2-Pyridyl	93–94	39	95% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.39	5.13	5.33	5.49	5.75
2,6-Dipyridyl	187–189	5	Ethyl acetate	$C_{25}H_{21}NO_6$	69.60	69.70	4.91	4.90	3.25	3.24

TABLE II

OXAZOLES



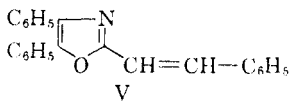
R	M.P.°	Yield, %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
α-Naphthyl	77.5–78.5	53	95% Ethanol	$C_{20}H_{15}NO$	84.20	84.46	5.30	5.54	4.91	5.23
β-Naphthyl	98.5–100	77	95% Ethanol	$C_{20}H_{15}NO$	84.20	84.65	5.30	5.83	4.91	5.20
2-Quinolyl	163–163.5	18	95% Ethanol	$C_{19}H_{14}NO_2$	79.66	79.58	4.93	5.09	9.79	10.33
6-Quinolyl	150–151	49	95% Ethanol	$C_{19}H_{14}NO_2$	79.66	79.64	4.93	5.29	9.79	10.42



I II III IV

esters shown in Table I. It was not found possible to cyclize all the esters listed in Table I into oxazoles.

The position of the methyl group in 2-methyl-4,5-diphenyloxazole on a carbon atom between an electronegative oxygen and an electronegative nitrogen suggested that the hydrogen atoms on the methyl group might be relatively active and might, therefore, condense with aldehydes such as benzaldehyde to produce the corresponding styryloxazoles, *e.g.*, (V). The four styryloxazoles prepared are listed in Table III.



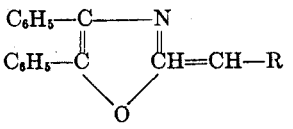
V

It does not appear that much effort has been made to introduce functional groups on carbon atoms 2, 4, or 5 in the oxazole ring system. The bromomethyl group was introduced in the 2-position of 4,5-diphenyloxazole by brominating 2-methyl-4,5-diphenyloxazole with *N*-bromosuccinimide. 4,5-Diphenyl-2-hydroxymethyloxazole was produced in good yield by hydrolysis of this 4,5-diphenyl-2-bromomethyloxazole in an aqueous alcohol solution of silver nitrate.

A method of introducing a carboxyl group in the 5-position of oxazoles has been discovered. For this purpose ethyl benzoylacetate was brominated, as in (I) following the general procedure. The bromo compound was converted to the ester, ethyl α-benzoyloxybenzoylacetate, which in turn was cyclized with ammonium acetate and acetic acid to ethyl 2,4-diphenylimidazole-5-carboxylate.[8] This imidazole was refluxed in aqueous potassium hydroxide solution and thus converted to 2,4-diphenyloxazole-5-carboxylic acid. To characterize

TABLE III

STYRYLOXAZOLES

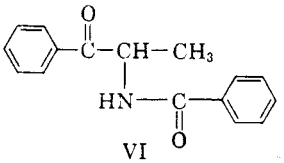


R	M.P.°	Yield, %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Phenyl	119–119.5	29	95% Ethanol	$C_{23}H_{17}NO$[a]					4.33	4.16
p-Anisyl	269–271	Trace	95% Ethanol	$C_{24}H_{19}NO_2$	81.55	81.31	5.42	5.13		
o-Hydroxyphenyl	216–217	62	95% Ethanol	$C_{23}H_{17}NO_2$	81.37	81.49	5.05	5.44	4.13	3.95
3,4-Methylenedioxyphenyl	142.5–143	Trace	95% Ethanol	$C_{24}H_{17}NO_3$	78.43	77.93	4.67	4.84		

[a] See reference (9).

further this acid it was converted to its *N,N*-dimethylaminopropyl amide.

In three instances when ring closures of esters of type III were attempted, side products other than the expected oxazoles were formed. When 2-benzoyloxy-1-phenyl-1-propanone was refluxed with ammonium acetate in acetic acid, not only was the expected oxazole (m.p. 74–75°) produced in good yield but another solid (m.p. 108–109°) was formed whose properties seem to coincide with those expected of 2-benzoylamido-1-phenyl-1-propanone (VI). The structure of VI was established from the



VI

infrared spectra and from the preparation of a semicarbazone derivative. The amide I band at 2.9 μ the amide II band at 6.0 μ and the carbonyl band at 5.82 μ were observed.

Similar observations were made when the starting esters were 1 - phenyl - 2 - (6 - quinolinecarboxoyloxy)-1-propanone and di-α-benzoylethyl pyridine-2,6-dicarboxylate.

EXPERIMENTAL[10]

The infrared absorption spectra were determined on a Perkin-Elmer Infracord in nujol mulls.

2-Bromo-1-phenyl-1-propanone. To 160.8 g. of propiophenone (1.2 moles) was added 150 ml. of anhydrous ether and the solution was stirred in an ice bath. To this cold solution was added 1.5 g. of anhydrous aluminum chloride. Over a 45-min. period, 192 g. (1.2 moles) of bromine was added. Additional ether (150 ml.) was added and the contents poured into water. The ether layer was washed with water until bromide ion was removed, the ether solution dried over anhydrous magnesium sulfate, filtered, and the ether removed under reduced pressure. There was obtained 228 g. (89%) of yellow oil boiling at 135–144° (19 mm.).

The esters in Table I were prepared by the model procedure illustrated below.

(10) All melting points are uncorrected.

2-Benzoyloxy-1-phenyl-1-propanone. Sodium benzoate, 14.4 g. (0.1 mole), 2-bromo-1-phenyl-1-propanone, 21 g. (0.1 mole), absolute ethanol, 125 ml., and 3 drops of concd. sulfuric acid were stirred and refluxed for 8 hr. The mixture was poured into 300 ml. of water with stirring and extracted with benzene. The benzene layer was washed with 200 ml. of 1% sodium hydroxide solution and twice with 200 ml. of water. The benzene layer was dried over anhydrous magnesium sulfate, filtered, and the benzene removed under reduced pressure. A white powder (14.9 g.) was obtained. A second crop amounted to 2.6 g. (69% yield). The product was recrystallized from ethyl acetate, m.p. 109–110°. Temnikova[11] reported 109°.

4,5-Diphenyl-2-methyloxazole. This compound was prepared according to the procedure of Davidson, Weiss, and Jelling.[8]

4,5-Diphenyl-2-styryloxazole. 4,5-Diphenyl-2-methyloxazole (4.7 g., 0.02 mole), benzaldehyde (15.7 g., 0.148 mole) and zinc chloride (1.4 g., 0.01 mole) were refluxed for 3 hr. under an atmosphere of nitrogen. The solution was cooled, benzene added and the mixture washed three times with water. The benzene layer was dried over anhydrous magnesium sulfate, filtered, and the benzene removed under reduced pressure. The unreacted benzaldehyde was removed by distillation (74° at 17.5 mm.). The unchanged oxazole was recovered by distillation (165–175° at 1 mm.). The residue in the distilling flask was dissolved in 95% ethanol and upon crystallization, 1.9 g. of a yellow-orange powder was obtained (29%). The product was recrystallized from 95% ethanol, m.p. 119–119.5° (previously reported 118.5°). This compound was previously prepared by direct cyclization by Dornow and Eichholz.[9]

Anal. Calcd. for $C_{23}H_{17}ON$: C, 85.43; H, 5.30; N, 4.33. Found: C, 86.05; H, 5.78; N, 4.16.

This general procedure was used for all the styryloxazoles shown in Table III.

2-Bromomethyl-4,5-diphenyloxazole. 4,5-Diphenyl-2-methyloxazole (11.8 g., 0.05 mole), *N*-bromosuccinimide (9 g., 0.05 mole), benzoyl peroxide, 2 g., and 40 ml. of dry carbon tetrachloride were refluxed for 6 hr. The mixture was cooled and the succinimide removed by filtration. The carbon tetrachloride was removed under reduced pressure leaving a viscous orange-red liquid, which was purified by distillation, b.p. 170° at 0.025 mm., micromelting point 104–106°.

Anal. Calcd. for $C_{16}H_{12}BrNO$: C, 61.16; H, 3.85. Found: C, 61.35; H, 4.13.

4,5-Diphenyl-2-hydroxymethyloxazole. 2-Bromomethyl-4,5-diphenyloxazole (15.7 g., 0.05 mole) was dissolved in 100 ml. of 95% ethanol. Silver nitrate, 10 g., was dissolved in 12 ml. of water and this solution was added to the swirled

(11) T. I. Temnikova and E. N. Kropacheva, *Doklady Acad. Nauk. S.S.S.R.*, **78**, 291 (1951). See *Chem. Abstr.*, 46, 2010^b (1952).

alcoholic solution. The mixture was refluxed on a steam bath for 1 hr., the silver bromide filtered and the ethanol removed on the steam bath. The yellow oil which remained was dissolved in ether and washed several times with water to remove the silver ion. The ether layer was dried over anhydrous magnesium sulfate, filtered, and the ether removed under reduced pressure. It distilled at 151–156° at less than 0.1 mm. to yield a viscous yellow liquid.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22. Found: C, 76.12; H, 5.53.

Ethyl α-bromobenzoylacetate. This was prepared in a manner similar to α-bromopropiophenone starting with ethyl benzoyl acetate. An 88% yield of a yellow oil boiling at 113–133° at 0.1 mm. was obtained.[12]

Ethyl-α-benzoyloxybenzoylacetate. This compound was prepared in a manner similar to 2-benzoyloxy-1-phenyl-1-propanone. The cream colored solid was recrystallized from 95% ethanol (75% yield), m.p. 61–62°.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.24; H, 5.17. Found: C, 69.65; H, 5.45.

Ethyl 2,4-diphenylimidazole-5-carboxylate. This compound was prepared according to the procedure of Davison, Weiss, and Jelling.[8] A cream colored solid (24 g.) was obtained. It was recrystallized from 95% ethanol, m.p. 166–167.5°.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.99; H, 5.52; N, 9.59. Found: C, 73.85; H, 5.67; N, 9.71.

2,4-Diphenyloxazole-5-carboxylic acid. Ethyl 2,4-diphenylimidazole-5-carboxylate (5.86 g., 0.02 mole), potassium hydroxide (1.6 g.), and 50 ml. of water were refluxed. The reflux condenser was equipped with a side arm for the removal of the condensate. The condensate was removed until a negative test was obtained for the presence of ethanol using ceric nitrate reagent. This required 1.75 hr. The solution was filtered and acidified with 5% hydrochloric acid. A white solid, 5.3 g., m.p. 222–223°, was obtained (quantitative).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.64; H, 4.41; N, 5.00.

N,N-Dimethylaminopropyl-2,4-diphenyloxazole-5-carboxamide. Potassium 2,4-diphenyloxazole-5-carboxylate (9.1 g., 0.03 mole) was passed through a 100 mesh sieve and dried overnight at 120°. This was added to 60 ml. of dry benzene in a three neck flask fitted with condenser, mercury seal stirrer, dropping funnel, and drying tube. Over a period of 20 min., a solution of 3.8 g. (0.03 mole) of oxalyl chloride in 15 ml. of dry benzene was added to the reaction mixture cooled in an ice bath. This cooled reaction mixture was stirred an additional 30 min., the ice bath removed, and the reaction mixture stirred an additional 3 hr. Dimethylaminopropylamine (3.2 g., 0.031 mole) was mixed with 15 ml. of dry benzene and added over a period of 20 min. The mixture was stirred for an additional 15 min., and then heated to boiling. The mixture was cooled and a 5% solution of hydrochloric acid was added. The dense yellow precipitate was filtered and the product dissolved in 5% hydrochloric acid solution. The acidic solution was filtered and upon neutralization with ammonium hydroxide, a white precipitate was obtained. The product was recrystallized from ethyl acetate whereupon long white needles separated, m.p. 161.5–163°.

(12) B. W. Howk and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 282 (1932).

Anal. Calcd. for $C_{21}H_{23}O_2N_3$: N, 12.02. Found: N, 11.65.

2,4-Diphenyl-5-methyloxazole. To 12.6 g. (0.05 mole) of 2-benzoyloxy-1-phenyl-1-propanone was added 19.3 g. (0.25 mole) of ammonium acetate in 50 ml. of glacial acetic acid. After the mixture had been refluxed for 1 hr., it was poured into ice and water and extracted with ether. The ether was washed with water and the ether layer dried over anhydrous magnesium sulfate. After filtration of the drying agent and evaporation of the ether the crude product was collected. Upon purification by repeated recrystallization from cyclohexane a buff-colored solid (m.p. 108–109.5°) separated. The 2,4-diphenyl-5-methyloxazole separated upon concentration of the mother liquors, m.p. 74–75°.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.70; H, 5.57; N, 5.95. Found: C, 81.80; H, 5.54; N, 5.58.

The other oxazoles listed in Table II were prepared in a similar manner.

The product, m.p. 108–109.5°, described above as separating first during the purification proved to be 2-benzoylamido-1-phenyl-1-propanone.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 75.60; H, 6.07; N, 5.82.

This compound was characterized by the infrared absorption spectra detailed in the discussion and by the preparation of a semicarbazone.

2-Benzoylamido-1-phenyl-1-propanone semicarbazone. The semicarbazone was prepared by the method of Shriner, Fuson, and Curtin,[13] m.p. 202–203°.

Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.77; H, 5.58. Found: C, 65.22; H, 5.63.

1-Phenyl-2-(6-quinolinecarboxoylamido)-1-propanone. This compound was isolated in a manner similar to 2-benzoylamido-1-phenyl-1-propanone during the preparation of 5-methyl-4-phenyl-2-(6-quinolyl)oxazole. This compound was purified by crystallization from ethanol, m.p. 195–197°.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.80; H, 5.70; N, 8.78.

This compound was characterized by the infrared spectra detailed in the discussion and by the preparation of a semicarbazone.

1-Phenyl-2-(6-quinolinecarboxoylamido)-1-propanone semicarbazone. This derivative was prepared in the usual manner, m.p. 209–211°.

Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C, 66.46; H, 5.30. Found: C, 66.72; H, 5.15.

N,N'-Bis(α-benzoylethyl)pyridine-2,6-dicarboxamide. This compound was isolated in a manner similar to 2-benzoylamido-1-phenyl-1-propanone during the attempted preparation of 2,6-bis[2-(5-methyl-4-phenyl)oxazolyl]pyridine, m.p. 211–213°.

Anal. Calcd. for $C_{25}H_{23}N_3O_4$: C, 69.90; H, 5.40; N, 9.78. Found: C, 70.36; H, 5.69; N, 9.86.

This compound was characterized by the infrared spectra detailed in the discussion.

ALBUQUERQUE, N. M.

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Ed., J. Wiley & Sons, Inc., New York, 1956.