[COMMUNICATION NO. 1865 FROM THE RESEARCH LABORATORIES, EASTMAN KODAK CO.]

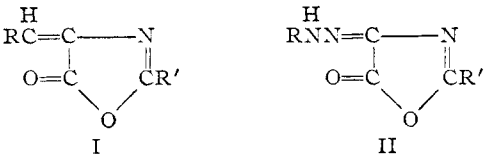
Rearrangement of 4-Arylazo-2-phenyloxazolin-5-ones: A New Synthesis of 1*H*-1,2,4-Triazoles

BY GEORGE W. SAWDEY

RECEIVED NOVEMBER 23, 1956

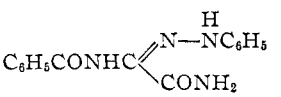
4-Phenylazo-2-phenyloxazolin-5-one is rapidly attacked by methanolic potassium hydroxide or methanolic ammonia, with the formation of 1,5-diphenyl-3-carboxy-1*H*-1,2,4-triazole and 1,5-diphenyl-3-carbamido-1*H*-1,2,4-triazole, respectively. On decarboxylation, the former gives 1,5-diphenyl-1*H*-1,2,4-triazole. The reactions appear to proceed by methanolysis of 4-phenyloxazolin-5-one and cyclization to the ester IV, with eventual hydrolysis or ammonolysis of the ester group.

Although the reaction of bases with 4-arylidene-2-oxazolin-5-ones (I), yielding α-acylaminoacrylic acids, has been widely studied,[1] little attention has been paid to the hydrolysis of the corresponding hydrazone derivatives II.



I

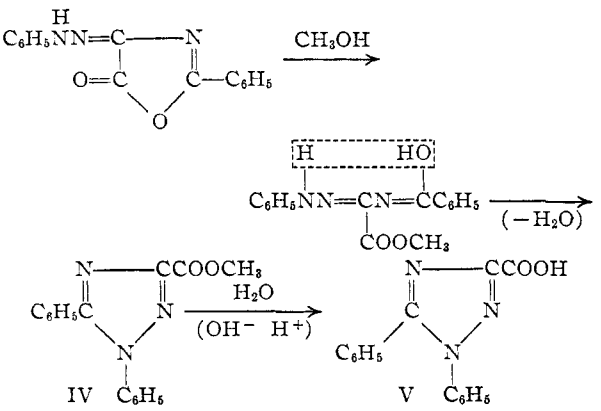
II



III

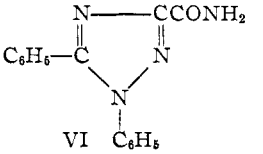
4-Phenylazo-2-phenyloxazolin-5-one, according to Kuskov,[2] decomposes in boiling alcoholic ammonia to give III. Kuskov's nitrogen analysis, 21.4%, does not agree with the calculated value for the composition just given, and in these Laboratories it was found that the expected hydrazone band, 360–370 mμ, is missing in the reaction product.

4-Phenylazo-2-phenyloxazolin-5-one is rapidly rearranged by methanolic potassium hydroxide to give a nearly quantitative yield of 1,5-diphenyl-3-carboxy-1*H*-1,2,4-triazole (V).



IV V

In alcoholic ammonia the amide is obtained instead of the free acid. This 1,5-diphenyl-3-carbamido-1*H*-1,2,4-triazole (VI) is, in the writer's opinion, the compound obtained by Kuskov. It is probable that in both reactions the ester is first formed and then saponified or ammonolyzed, depending upon the reaction conditions. The rearrangement is similar to that occurring in the hydrolysis of β-methylglutaconic anhydrides to form



VI

pyridazones.[3] The identity of V was established by comparison with an authentic sample prepared by the method of Bladin.[4] Compound V undergoes decarboxylation at the melting point, *ca.* 180°, to form 1,5-diphenyl-1*H*-1,2,4-triazole, m.p. 90–91°.[5] This compound was characterized by its picrate, m.p. 139–140°, and by comparison with a sample prepared by the method of Young.[6] Compound V was esterified with methanol to give the ester obtained by Bladin[7] from the silver salt and methyl iodide. Refluxing the ester with methanolic ammonia gave a product identical to that from II and boiling methanolic ammonia (VI). A mixed melting point showed no depression.

Experimental

Preparation of 4-Phenylazo-2-phenyloxazolin-5-one.—4-Phenylazo-2-phenyloxazolin-5-one can be satisfactorily prepared by the method of Kuskov[2] or as follows:

To a solution of 18.6 g. (0.2 mole) of aniline in 200 cc. of glacial acetic acid was added 40 cc. of concentrated hydrochloric acid, then, dropwise, 30.4 g. (0.23 mole) of isoamyl nitrite at room temperature. To the diazonium mixture was added 30 g. of anhydrous sodium acetate. Forty-five grams (0.25 mole) of hippuric acid was heated in 200 cc. of acetic anhydride until a clear solution was obtained. This solution was cooled to room temperature and added, slowly with agitation, to the diazonium mixture. The mixture was cooled and the precipitate was collected by suction filtration. Recrystallization from acetone gave 38.2 g., 72% of the theoretical quantity, of orange-yellow needles, m.p. 202–203°.

Reaction of 4-Phenylazo-2-phenyloxazolin-5-one with Methanolic Potassium Hydroxide.—Ten grams (0.038 mole) of 4-phenylazo-2-phenyloxazolin-5-one was dissolved in 200 cc. of methanol containing 10 cc. of 20% aqueous potassium hydroxide. After stirring 5 minutes at room temperature, the pale yellow solution was neutralized to litmus with hydrochloric acid and evaporated to crystallization. Recrystallization from benzene gave 9.1 g., 91% of the theoretical quantity, of blunt needles, m.p. 181° dec.

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.9; H, 4.2; N, 15.8. Found: C, 68.0; H, 4.2; N, 15.8.

(1) H. E. Carter, "Organic Reactions," Roger Adams, editor, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 214 *et seq.*

(2) V. K. Kuskov, *J. Gen. Chem.* (*U.S.S.R.*) (English Translation, Ed.), **21**, 165 (1951).

(3) R. H. Wiley and C. H. Jarboe, Jr., THIS JOURNAL, **77**, 403 (1955).

(4) J. A. Bladin, *Ber.*, **22**, 796 (1889).

(5) In common with previous workers, we found here in these Laboratories that this decarboxylation gave a low yield of triazole. One of the products has been tentatively identified as 3,3'-bis-(1*H*-1,2,4-triazole).

(6) G. Young, *J. Chem. Soc.*, **67**, 1063 (1895).

(7) J. A. Bladin, *Ber.*, **22**, 801 (1889).

Reaction of 4-Phenylazo-2-phenyloxazolin-5-one with Methanolic Ammonia.—Seven grams (0.026 mole) of 4-phenylazo-2-phenyloxazolin-5-one was dissolved in 200 cc. of methanol and 200 cc. of 25% ammonium hydroxide. The solution was heated under reflux for 5 minutes and then evaporated to crystallization. Recrystallization from methanol gave 5.5 g., 79.7% yield, of platelets melting at 198–199°.

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.2; H, 4.6; N, 21.2. Found: C, 68.2; H, 4.5; N, 21.2.

Decarboxylation of 1,5-Diphenyl-3-carboxy-1*H*-1,2,4-triazole.—Five grams (0.019 mole) of 1,5-diphenyl-1*H*-1,2,4-triazole from the preceding experiment was heated to 185° in an oil-bath until the decarboxylation started. The temperature was then lowered and held at 170° until evolution of gas had ceased. The resinous residue was extracted twice with 100-cc. portions of cyclohexane. Evaporation of the solvent left 2.1 g. of crude material melting at 76–80°. Recrystallized from water, 1.6 g., 38%, of colorless needles, m.p. 90–91°, was obtained.

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 76.0; H, 5.0; N, 19.0. Found: C, 75.8; H, 4.9; N, 18.6.

The picrate melted at 139–140°; Thompson reports 140–141°.[8]

Esterification of 1,5-Diphenyl-3-carboxy-1*H*-1,2,4-triazole.—Two grams (0.0075 mole) of 1,5-diphenyl-3-carboxy-1*H*-1,2,4-triazole was refluxed 1 hr. with 20 cc. of methanol containing a drop of sulfuric acid. The reaction mixture was poured into water and the crude ester collected. Recrystallization from methanol gave 1.4 g., 68%, of colorless platelets, m.p. 158–159°.

Ammonolysis of the Ester.—One gram (0.0036 mole) of the ester was refluxed 1 hr. with 20 cc. of methanol and 20 cc. of 25% ammonium hydroxide. The reaction mixture was evaporated nearly to dryness. The precipitate was collected and was recrystallized from methanol; yield 0.59 g., 62%, of colorless platelets, m.p. 198–199°. This product gave no depression in melting point when mixed with the product of direct ammonolytic rearrangement of 4-phenylazo-2-phenyloxazolin-5-one.

1,5-Diphenyl-3-carbamido-1*H*-1,2,4-triazole has been previously prepared by Bladin[7] by oxidation of the corresponding cyanotriazole.

(8) Q. E. Thompson, THIS JOURNAL, **73**, 5914 (1951).

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. XIV.[1] Some ω-Fluoroalkyl Nitrogen Compounds

BY G. J. O'NEILL AND F. L. M. PATTISON

RECEIVED OCTOBER 18, 1956

Some ω-fluoroalkyl isocyanates, isothiocyanates, urea derivatives and barbiturates have been prepared and their toxicities determined. None of the compounds were outstandingly toxic. The activity of the fluorobarbiturates as depressants of the central nervous system was less than that of their non-fluorinated analogs.

In continuation of the study of toxic fluorine compounds, certain nitrogen compounds were prepared and examined (Table I). These included: three isocyanates, two isothiocyanates and four urea derivatives, all of which were prepared for comparison with the corresponding ω-fluoroalkylamines[2]; and two ω-fluoroalkylbarbituric acids,[3] for testing as depressants of the central nervous system.

Preparation.—The ω-fluoroalkyl isocyanates were prepared by means of the Curtius rearrangement.[5,6] ω-Fluorocarboxylic acid chlorides,[7] available in high yield from the corresponding acids,[8] were treated with activated sodium azide[9] to form the acid azides, which in turn were rearranged to the isocyanates. 2-Fluoroethyl, 3-fluoropropyl and 4-fluorobutyl isocyanates were thus obtained in yields of 44, 49 and 85%, respectively. Fluoromethyl isocyanate could not be prepared by this procedure; the product of the reaction boiled over a wide temperature range and, on standing, deposited a high melting solid, which was insoluble in common organic solvents. An attempt was then made to form the fluoromethyl derivative using fluoroacetic anhydride instead of fluoroacetyl chloride, but the results were equally indefinite. These observations suggest that fluoromethyl isocyanate is inherently unstable.

Since prolonged contact with air resulted in polymerization and urea formation, the isocyanates were distilled in an atmosphere of nitrogen and handled in a closed system. For this purpose, an assembly was devised which served both as a receiver on the Todd still and as a manifold for transferring the materials to sealed ampoules.

The N-ω-fluoroalkyl-N′-phenylureas, prepared as a means of characterizing the ω-fluoroalkyl isocyanates, were obtained from the latter by treatment with aniline. N,N′-Bis-4-fluorobutylurea was prepared from 4-fluorobutyl isocyanate by treatment with water.

The ω-fluoroalkyl isothiocyanates were prepared[10,11] from the corresponding amines by conversion to the sodium dithiocarbamates, followed by treatment with ethyl chloroformate. It was necessary to carry out these reactions at −15° to avoid the formation of impurities which co-distilled with the main product. 5-Fluoroamyl and 6-fluorohexyl isothiocyanates were thus obtained in yields of 56 and 48%, respectively.

The two ω-fluoroalkylbarbituric acids were prepared[3] in low yield from diethyl ethylmalonate by

(1) Issued as DRB Report No. SW-32. Part XIII, *Can. J. Chem.*, **35**, 141 (1957).

(2) F. L. M. Pattison, W. C. Howell and R. W. White, THIS JOURNAL, **78**, 3487 (1956).

(3) F. L. M. Pattison, *Nature*, **174**, 737 (1954).

(4) W. F. Bruce and R. deV. Huber, THIS JOURNAL, **75**, 4668 (1953); U. S. Patent 2,721,201 (Oct. 1955).

(5) J. W. Boehmer, *Rec. trav. chim.*, **55**, 379 (1936).

(6) P. A. S. Smith, *Organic Reactions*, **3**, 337 (1946).

(7) F. L. M. Pattison, R. R. Fraser, G. J. O'Neill and J. F. K. Wilshire, *J. Org. Chem.*, **21**, 887 (1956).

(8) F. L. M. Pattison, S. B. D. Hunt and J. B. Stothers, *ibid.*, **21**, 883 (1956).

(9) J. Nelles, *Ber.*, **65B**, 1345 (1932).

(10) K. H. Slotta and H. Dressler, *ibid.*, **63B**, 888 (1930).

(11) M. L. Moore and F. S. Crossley, *Org. Syntheses*, **21**, 81 (1941).