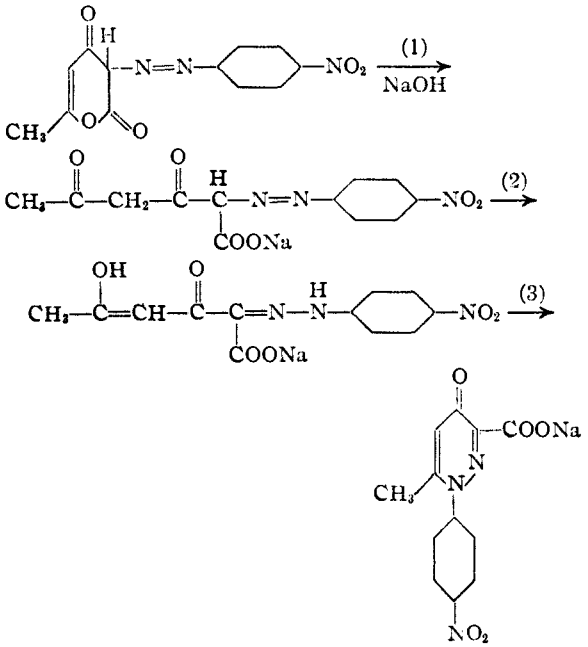
[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORY OF GENERAL ANILINE AND FILM CORPORATION]

A New Synthesis of 4-Pyridazones

BY JACK F. MORGAN

During an investigation of azo dyes derived from substituted 1,2-pyran-2,4(3)-diones, it was observed that many of these dyes gradually fade in color when heated in dilute alkaline solutions. For example, when an aqueous alcohol solution of 6-methyl-3-*p*-nitrophenylazo-1,2-pyran-2,4(3)-dione was refluxed for one to two hours with an equi-molar amount of sodium hydroxide, a good yield of a very pale yellow carboxylic acid resulted. This acid had the same empirical formula as the original dye as shown by analysis and neutralization equivalent. Obviously, some sort of rearrangement of the original molecule had taken place. The apparent course of the reaction is shown below.



The assumed product, 1,4-dihydro-6-methyl-1-(*p*-nitrophenyl)-4-oxo-3-pyridazinecarboxylic acid, is in agreement with the experimental product in regard to empirical formula, neutralization equivalent, expected color and expected melting point. In addition, the steps outlined above represent a logical sequence of events when considered in the light of known facts regarding the chemical behavior of similar compounds.

Step 1.—The 1,2-pyran-2,4(3)-dione ring is quite stable toward acid hydrolysis but is cleaved at the oxygen bridge in hot alkaline solutions.

Step 2.—Azo compounds derived from aliphatic active methylene compounds like acetoacetic ester are in tautomeric equilibrium with the corresponding hydrazones.[1]

(1) Frank C. Whitmore, "Organic Chemistry," D. Van Nostrand Co., New York, N. Y., p. 755.

Step 3.—Aryl hydrazones of this general type are known to undergo ring closure to form pyridazones.[2]

The conversion of the azo compound to the pyridazone may be carried out about equally well in either aqueous–alcohol or water alone. The alkali used may be sodium hydroxide, sodium carbonate or sodium bicarbonate. The reaction proceeds satisfactorily when excessive amounts of sodium bicarbonate are used though too much sodium hydroxide may have a harmful effect on yields.

The main advantage of the method of synthesis under discussion is that it leads to products not available by other reactions. Thus all the pyridazones prepared by this method were new and no other method was available for their preparation. This pyridazone synthesis seems to be fairly general in application though an exhaustive study was not made to determine its limitations. The reaction did fail when applied to 3-(2,5-dichlorophenylazo)-4-hydroxycoumarin.

The azo compounds required as starting materials were easily prepared from 1,2-pyran-2,4(3)-diones and the appropriate diazo compounds in either alkaline or slightly acid solution. The corresponding pyridazones are most conveniently prepared without isolation or purification of the azo intermediates.

General methods for the preparation of the 1,2-pyran-2,4(3)-diones used in this work are adequately described in the literature.[3,4,5,6] One of these compounds, 6-ethyl-1,2-pyran-2,4(3)-dione (m. p. 107–108°) had not previously been described in the literature. This product was prepared in 70% yield from 6-ethyl-3-propionyl-1,2-pyran-2,4(3)-dione[4,5] by the method of Collie.[3]

Experimental

The general procedure for preparing 4-pyridazones is illustrated by the following example which includes the preparation of the azo intermediate.

1,4-Dihydro-6-methyl-1-(*o*-nitrophenyl)-4-oxo-3-pyridazinecarboxylic Acid.—*o*-Nitroaniline (11 g., 0.08 mole) was dissolved in a hot solution of concentrated hydrochloric acid (40 ml.) and water (50 ml.), poured onto ice and diazotized in the usual manner by rapid addition of a slight excess of sodium nitrite solution. This solution (250 ml.) was then added to a stirred solution of 6-methyl-1,2-pyran-2,4(3)-dione (10.8 g., 0.085 mole) and sodium carbonate (35 g.) in water (550 ml.). The coupling reaction was complete within fifteen minutes. The resultant slurry was stirred and heated at the reflux temperature for two and one-half hours. The hot clear solution was neutralized (*p*H 6–7) with acetic acid, treated with charcoal and filtered. The filtrate was then acidified (*p*H 2) with hydrochloric acid and cooled in ice. The

(2) A. Sonn, *Ann.*, **518**, 290 (1935).
(3) J. N. Collie, *J. Chem. Soc.*, **59**, 609 (1891).
(4) von Pechmann and Neger, *Ann.*, **273**, 201 (1893).
(5) Deshapande, *J. Indian Chem. Soc.*, **9**, 303–307 (1932).
(6) Panly and Lockemann, *Ber.*, **48**, 31 (1915).

TABLE I

1,4-DIHYDRO-4-OXO-3-PYRIDAZINECARBOXYLIC ACIDS

Substituent in 1-Position	6-Position	Yield,[a] %	M. p.,[b] °C., %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Nitrophenyl	Methyl	72	224[a]	52.37	3.30	15.27	52.36	3.24	15.14
3-Nitrophenyl	Methyl	87	224	52.37	3.30	15.27	52.97	3.69	15.46
4-Nitrophenyl	Methyl	92	247	52.37	3.30	15.27	51.96	3.52	15.15
2,5-Dichlorophenyl	Methyl	78	209	48.18	2.70	9.37	48.22	2.76	9.29
4-Chlorophenyl	Ethyl	87[c]	160			10.05			10.18
4-Chlorophenyl	Ethyl	85	158			10.05			10.11
3-Nitrophenyl	Phenyl	82	206			12.50			12.25
2-Chlorophenyl	Phenyl	63	218			8.62			8.48

[a] Crude product. [b] Recrystallized from alcohol or acetic acid. Melting points are uncorrected. [c] Prepared in 50% alcohol solution.

pale yellow crystals were removed by filtration, washed with water and dried to obtain 15.8 g. (72%) of 1,4-dihydro-6-methyl-1-(*o*-nitrophenyl)-4-oxo-3-pyridazinecarboxylic acid melting at 224° (uncor.).

Summary

A new synthesis of 4-pyridazones has been described. Alkaline hydrolysis of 6-alkyl-3-arylazo-1,2-pyran-2,4(3)-diones results in cleavage of the pyran-2,4(3)-dione nucleus followed by rearrangement to 1,4-dihydro-6-alkyl-1-aryl-4-oxo-3-pyridazinecarboxylic acids.

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Succinic Acid Derivatives of 4-Nitro-4′-aminodiphenylsulfone and of 4,4′-Diaminodiphenylsulfone

BY HUGO BAUER

Recent studies in experimental tuberculosis carried on in this institute[1] have demonstrated that potentiation is obtained in combined therapy with streptomycin and certain derivatives of 4,4′-diaminodiphenylsulfone. The presence of one free amino group appears to be essential for good action. It seemed desirable to test the chemotherapeutic properties of *n*-acylamide and ester derivatives. Compounds of this type were obtained by the preparation of succinic acid derivatives of diaminodiphenylsulfone. Furthermore, derivatives of succinic acid have been found to be active in tuberculosis.[2]

The action of succinic acid or succinic anhydride upon 4,4′-diaminodiphenylsulfone has been reported to lead to the formation of a disubstituted product.[3] An attempt was made to obtain the monosubstituted product by heating equivalent amounts of diaminodiphenylsulfone with succinic acid. From the reaction mixture 4-amino-4′-succinimidodiphenylsulfone (II) could be isolated in poor yield (12–13% of the calcd.).

Better results were obtained by starting with 4-nitro-4′-aminodiphenylsulfone. At a temperature of about 220°, it combines easily with succinic anhydride, yielding 4-nitro-4′-succinimidodiphenylsulfone (I). The products obtained from I by hydrolysis, esterification, ammonolysis and reduction are shown in Table I. The nitro group was reduced with hydrogen at atmospheric pressure in presence of Raney nickel catalyst, with excellent yields.

Compound II was tested[1c] alone and in combination with streptomycin in experimental tuberculosis in guinea pigs. The chemotherapeutic effectiveness was in the same range as that found for promin, but inferior to that of 4-amino-4′-*n*-propylaminodiphenylsulfone.[1b,c] Compound VII showed approximately the same activity in experimental tuberculosis as compound II.[4]

Compounds II, IV, VII and IX, also were active when tested in experimental pneumococcus infection in mice.[5]

Experimental

4-Nitro-4′-succinimidodiphenylsulfone (I).—A mixture of 27 g. of 4-nitro-4′-aminodiphenylsulfone and of 12 g. of succinic anhydride was heated in an oil-bath at 220° for thirty minutes. A clear orange melt resulted which crystallized upon cooling. The crude product melted at 230–232°. From hot glacial acetic acid cream-colored needles (29.5 g.) of m. p. 240–241° were obtained (calcd. 35 g.). The substance is soluble in hot acetone, hot glacial acetic acid, sparingly in hot dioxane.

4-Amino-4′-succinimidodiphenylsulfone (II).—Either 4,4′-diaminodiphenylsulfone or compound (I) was used

(1) M. I. Smith, *et al.*, (a) *Pub. Health Repts.*, **60**, 1129 (1945); (b) *Am. Rev. Tuberc.*, **55**, 366 (1947); (c) *Proc. Soc. Exptl. Biol. and Med.*, **64**, 261 (1947).

(2) V. C. Barry and P. A. McNalley, *Nature*, **156**, 48 (1945).

(3) W. H. Gray and B. C. Platt, *J. Chem. Soc.*, 42 (1942); M. S. Kharasch and O. Reinmuth, U. S. Patent 2,268,754, Jan. 6, 1942; H. Heymann and L. F. Fieser, THIS JOURNAL, **67**, 1979 (1945).

(4) Unpublished data; personal communication by W. T. McClosky of this Laboratory.

(5) Unpublished data; personal communication by J. M. Junge of this Laboratory.