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.

EASTON, PENNSYLVANIA RECEIVED FEBRUARY 19, 1948

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, UNITED STATES PUBLIC HEALTH SERVICE]

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).

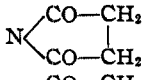
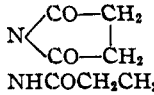
(2) V. C. Barry and P. A. McNalley, *Nature*, **156**, 48 (1945).

(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.

TABLE I

No.	R	R′	Yield % of calcd.	M. p., uncor., °C.	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
I[b]	NO_2		86	240–241	53.33	53.46	3.36	3.61	7.78	7.54	8.90	8.94
II	NH_2		12.2 83	227–228	58.17	58.26	4.27	4.31	8.48	8.40	9.71	9.81
III[c]	NO_2	$NHCOCH_2CH_2CO_2H$	96.5	205 d.	50.79	50.93	3.73	4.01	7.40	7.20	8.47	8.53
IV[d]	NH_2	$NHCOCH_2CH_2CO_2H$	65	185–186	55.16	55.06	4.63	4.79	8.04	7.92	9.20	9.08
V[c]	NO_2	$NHCOCH_2CH_2CO_2C_2H_5$	95	223–224					6.89	6.67	7.89	7.79
VI[c]	NO_2	$NHCOCH_2CH_2CO_2CH_3$	80	225–226							8.17	8.10
VII	NH_2	$NHCOCH_2CH_2CO_2C_2H_5$	90	178	57.43	57.49	5.36	5.54	7.44	7.17	8.52	8.42
VIII	NO_2	$NHCOCH_2CH_2CONH_2$	95	242	50.92	50.31	4.01	4.35	11.14	10.83	8.50	8.48
IX	NH_2	$NHCOCH_2CH_2CONH_2$	90	140	53.92	53.90	5.09	5.12	11.79	11.26	9.00	8.84
X[b]	NO_2	$NHCOCH_2CH_2CONHC_6H_5$	62	225–226	58.27	58.24	4.22	4.40	9.27	9.01	7.07	6.91
XI	NH_2	$NHCOCH_2CH_2CONHC_6H_5$	85	257							7.68	7.58
XII[b]	NO_2	$NHCOCH_2CH_2CONHC_6H_{11}$	86	275–276							6.98	6.98
XIII	NH_2	$NHCOCH_2CH_2CONHC_6H_{11}$	94	241							7.46	7.37

[a] I am indebted to Mr. C. A. Kinser for the determination of carbon and hydrogen and (in part) of nitrogen. [b] Cream crystals. [c] Pale yellow crystals. [d] See ref. 6. [e] $+{}^1/_2H_2O$: m. p. 140–143°, H_2O calcd. 2.52, found 2.55; $+C_2H_5OH$: m. p. 185–186°, C_2H_5OH, calcd. 11.66, found 11.63; $+HCl + 2H_2O$: m. p. 202–204°, Cl calcd. 8.42, found 8.25.

as starting material. The first procedure was rather unsatisfactory and was abandoned in favor of the second.

1. A mixture of finely powdered 4,4′-diaminodiphenylsulfone (50 g.) and succinic acid (24 g.) was heated in an oil-bath at 200–210° for two to three hours, until the evaporation of water ceased and a homogeneous liquid was formed. After cooling, the cake was powdered. The reaction product consisted of a mixture of mono- and disubstituted derivatives, besides unreacted diaminodiphenylsulfone. Eight batches were combined and extracted with three liters of warm acetone. II was isolated by fractional crystallization from acetone and acetone-alcohol mixture. The fractions of m. p. 200–230° were combined (about 85 g.) and recrystallized from acetone, thus giving about 65 g. of material of m. p. 220–223°. The melting point was raised to 226–227° by repeated recrystallization.

Using succinic anhydride instead of succinic acid offered no advantage in preparing the compound.

2. Compound I (5 g.) was suspended in 100 cc. of 95% alcohol and shaken with Raney nickel catalyst in a hydrogen atmosphere at atmospheric pressure and room temperature. The calculated amount of hydrogen was taken up in seven to eight hours. (The time should be considerably shortened with application of higher pressures.) The reaction product was brought in solution by heating with the addition of acetone. From the filtered and concentrated solution, 3.8 g. of beautiful needles of m. p. 226–227° were obtained (83% of the calcd.). After recrystallization from acetone, the m. p. was 227–228°.

4-Nitro-4′-β-carboxypropionylaminodiphenylsulfone (III): Hydrolysis of I.—Compound I (7.2 g., $^1/_{50}$ mole) was heated to boiling with 100 cc. of 95% alcohol. With vigorous shaking, 5 cc. of 5 *N* sodium hydroxide solution (calcd. 4.0 cc.) was added until an almost complete solution was formed. The orange solution including a small amount of insoluble material, was cooled with running water, whereupon the sodium salt crystallized as a white crystalline powder. The sodium salt was isolated, dissolved in water, the solution was filtered and acidified with 2 *N* hydrochloric acid. A colorless, voluminous precipitate of the free acid separated which, after filtering and drying, weighed 7.3 g. and melted at 200–202°.

From alcohol clusters of fine, pale yellow needles of m. p. 205° were obtained.[6] The compound is soluble in sodium hydrogen carbonate solution. When heated with an excess of sodium hydroxide, it is split with formation of 4-nitro-4′-aminodiphenylsulfone.

4-Amino-4′-β-carboxypropionylaminodiphenylsulfone (IV).—Compound III was reduced with Raney nickel catalyst and hydrogen in alcoholic suspension. From alcohol colorless crystals, containing alcohol of crystallization, of m. p. 185–186° were obtained. The alcohol can be removed by heating at 110°. From hot water the compound crystallizes with 0.5 mole of water, showing m. p. 140–143°. It is soluble in ammonia; from this solution it is precipitated by dilute hydrochloric acid and dissolved by an excess of acid, when freshly precipitated. After short standing the base crystallizes again. The hydrochloride was obtained by addition of an excess of concentrated hydrochloric acid. It contained two moles of water and melted at 202–204°. For analysis the water was removed by heating *in vacuo* at 100° for two hours.

A yellow water-insoluble diazo compound was formed by diazotization of the suspension of IV in 2 *N* hydrochloric acid, which coupled with β-naphthol with a deep red color.

Compound IV was also obtained by hydrolysis of II with about 40% yield, when heated with 4 *N* hydrochloric acid for five minutes. Succinic acid was partially split off.

4-Nitro-4′-β-carboethoxypropionylaminodiphenylsulfone (V): 1. Alcoholysis of I.—Compound I (5 g.) was heated in a sealed tube with absolute alcohol and ten drops of concentrated hydrochloric acid at 200° for six hours. Small yellow crystals formed. The product was boiled with alcohol, the insoluble residue weighed 2.8 g. It was recrystallized from hot pyridine with addition of alcohol. Pale yellow crystals (2.3 g.) were obtained, m. p. 222–223°.

2. Esterification of III.—Compound III (10 g.) was suspended in 150 cc. of absolute ethyl alcohol and, without cooling, dry hydrochloric acid gas was passed through until the mixture was saturated. After cooling, the reaction mixture was poured in ice water and filtered. The crystalline product was suspended in water containing a little ammonia, filtered and dried; yield 10.7 g., m. p. 223°. When recrystallized as before it melted at 223–224°.

4-Nitro-4′-β-carbomethoxypropionylaminodiphenylsulfone (VI) was prepared according to the procedure V 2.

4-Amino-4′-β-carboethoxypropionylaminodiphenylsulfone (VII).—The procedure II 2 was used.

4-Nitro-4′-β-carbamylpropionylaminodiphenylsulfone (VIII): Ammonolysis of I.—Ammonolysis of I with al-

(6) Previously prepared by Q. Mingoia and F. Berti, *Arquiv. biol. (Sao Paolo)*, **27**, 55 (1943); *C. A.*, **39**, 2057 (1945); a m. p. of 194° is reported.

coholic ammonia gave the succinamide derivative, with admixture of the ethyl ester V.

Compound I (14.4 g.), finely powdered, was allowed to stand in saturated alcoholic ammonia for six days, with occasional shaking. The appearance changed while the heavy crystalline powder became more voluminous. When all heavy material had disappeared, the product was filtered off and washed with alcohol. It melted at 228–232°. After recrystallization from a mixture of pyridine and acetone it melted at 240°. The admixture of the ester was detected only after reduction (see below).

A pure preparation was obtained by ammonolysis with concentrated aqueous ammonium hydroxide. Compound I was warmed with 28% ammonium hydroxide in a stoppered bottle at 60° for two days. The product was washed with water and crystallized from pyridine. To remove pyridine of crystallization, the crystals were suspended in warm alcohol; the volume of the material increased considerably. After washing with alcohol and drying, the m. p. was 242°.

The compound was not soluble in alcohol or acetone, sparingly soluble in dioxane or glacial acetic acid, soluble in hot pyridine.

4-Amino-4′-β-carbamylpropionylaminodiphenylsulfone (IX).—Compound VIII, obtained by alcoholic ammonolysis, was reduced with Raney nickel catalyst and hydrogen in alcoholic suspension. The crude reduction product melted at 135°. Most of it was soluble in hot water. When recrystallized from hot water, containing a little ammonia, colorless fine needles were obtained of m. p. 140°. The solubility in water at 26° was 0.4%. The water-insoluble material was identified with VII by melting point and analysis.

4-Nitro-4′-β-phenylcarbamylpropionylaminodiphenylsulfone (X).—Compound I (13.5 g.) was refluxed with aniline for fourteen hours. After dilution with alcohol, 10.5 g. of material m. p. 205–210° was isolated. From hot acetone (charcoal) cream crystals of m. p. 225–226° were obtained. It is sparingly soluble in hot alcohol.

4-Amino-4′-β-phenylcarbamylpropionylaminodiphenylsulfone (XI) was prepared from X using the procedure II 2.

4-Nitro-4′-β-cyclohexylcarbamylpropionylaminodiphenylsulfone (XII).—Compound I (7.2 g.) was refluxed with cyclohexylamine for five hours. The yield was 8.7 g., the m. p. 276°. Recrystallized from glacial acetic acid, the cream needles melted at 275–276°. The compound was not soluble in alcohol or acetone, soluble in hot pyridine and hot glacial acetic acid.

4-Amino-4′-β-cyclohexylcarbamylpropionylaminodiphenylsulfone (XIII) was prepared from XII using the procedure II 2.

Summary

The preparation of succinic acid derivatives of 4-nitro-4′-aminodiphenylsulfone and of 4,4′-diaminodiphenylsulfone has been described. 4-Amino-4′-succinimidodiphenylsulfone (II) and 4′-amino-4′-β-carboethoxypropionylaminodiphenylsulfone (VII) were tested in experimental pneumonia and tuberculosis and found to be active. 4-Amino-4′-β-carboxypropionylaminodiphenylsulfone (IV) and 4-amino-4′-β-carbamylpropionylaminodiphenylsulfone (IX) were also active in experimental pneumococcus infections in mice.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STATE UNIVERSITY OF IOWA

Kinetic Analysis of Irreversible Consecutive Reactions

BY JEN-YUAN CHIEN

The kinetics of consecutive reactions have been of considerable interest since even simple chemical change may go through a number of intermediate steps. When the rate constants of each step are comparable in magnitude, the integration of the kinetic equations presents considerable difficulties. Especially when reactions of high order in the intermediate steps are involved, the resulting system of non-linear differential equations can only be solved by successive approximations. Hill[1] has recently outlined a general scheme of such methods, but the amount of labor required would be tremendous because of the fact that the rate constants themselves are the unknown parameters sought. In this paper, certain types of two step irreversible consecutive reactions are considered, where the solution in closed form has been found. These solutions serve as an extension to the summary of formulas compiled by Moelwyn-Hughes.[2]

(1) T. L. Hill, THIS JOURNAL, **64**, 465 (1942).

(2) E. A. Moelwyn-Hughes, "Physical Chemistry," Cambridge University Press, Appendix 9, 1940, pp. 633–641.

Integration of the Kinetic Equations

I. Uni-unimolecular Reaction.—The general solution for a unimolecular reaction chain of any number of steps has been found.[3] For the particular case of a two-step reaction

$$\mathrm{A} \xrightarrow{k_1} \mathrm{B} \xrightarrow{k_2} \mathrm{C} \qquad (\mathrm{I})$$

starting with a_0 mole of A, the solution may be expressed in terms of a dimensionless variable τ and a dimensionless parameter κ in the following form, where A, B and C are concentrations of A, B and C, respectively, at t.

$$\left.\begin{aligned} A &= a_0\tau \\ B &= a_0\left(\frac{\tau^\kappa - \tau}{1-\kappa}\right) \\ C &= a_0 - A - B \end{aligned}\right\} \quad (1)$$

where

$$\tau = e^{-k_1 t} \text{ and } \kappa = k_2/k_1$$

II. Uni-bimolecular reaction.—Two separate cases are to be considered, one with a single

(3) H. Bateman, *Proc. Camb. Phil. Soc.*, **15**, 423 (1910).