[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Some Sulfanilamide Derivatives of Substituted Ethylenediamines[1,2]

BY GEORGE B. BUTLER AND FRANCIS N. MCMILLAN

The purpose of this investigation was to utilize certain readily available derivatives of ethylenediamine in the preparation of sulfanilamide derivatives for study of their pharmacological action. Amines of the type used may be readily prepared by catalytic reduction of the aliphatic nitroamines derivable from secondary amines, formaldehyde and 2-nitropropane.

Johnson[3] treated secondary amines with formaldehyde and 2-nitropropane to obtain several compounds of the type used in this work. This author also reduced the nitroamines produced to the corresponding amines under hydrogen pressure in presence of Raney nickel. However, as far as can be determined, these compounds or similar derivatives have not been investigated from the standpoint of preparation of sulfanilamide derivatives.

In the preparation of N-(2-nitro-2-methylpropyl)-morpholine and N-(2-nitro-2-methylpropyl)-piperidine, Johnson[3] isolated and purified the nitro alcohol which subsequently reacted with the amine, about six days being required for completion of the reaction. In this investigation, it was found that the reaction could be completed resulting in good yields of the products, in about three hours, thus avoiding the isolation and purification of the intermediate product.

Experimental

Preparation of Nitroamines.—In a three-liter, three-necked flask, fitted with a condenser, a stirrer, a thermometer immersed in the reaction mixture and a dropping funnel, was placed one mole of 2-nitropropane, one mole of the secondary amine and 300 ml. of dioxane. The contents of the flask was cooled to 5° by means of an ice-bath. A mixture of one equivalent of 37% formaldehyde and 40 ml. of 2% sodium hydroxide solution was added at such a rate that the temperature of the reaction mixture did not exceed 10°. The mixture was stirred for one hour after completion of the addition and then heated for one hour on a steam-bath. The reaction mixture was cooled to 20° and 500 cc. of cold water was added. The oily layer was separated, dried over anhydrous calcium sulfate, and fractionated under reduced pressure.

The following compounds were prepared in the percentage yields indicated: N-(2-nitro-2-methylpropyl)-morpholine, 65%; N-(2-nitro-2-methylpropyl)-piperidine, 76.5%; and N-(2-nitro-2-methylpropyl)-diethylamine, 74%. The diethyl derivative has not been previously reported and was characterized as follows: b. p. 63–64° (2 mm.). *Anal.* N found 15.95, calcd. 16.10; $n^{25}D$ 1.4393; d^{25}_4 0.9504; molar refrac. found 48.32, calcd. 48.52.

Reduction of Nitroamines.—The method described by Senkus[4] for the reduction of aliphatic nitro compounds was employed for preparation of the amine derivatives, with the exception that pressures up to 1000 p. s. i. were used. The following compounds were prepared in the percentage yields indicated by this method: N-(2-amino-2-methylpropyl)-morpholine, 71%; N-(2-amino-2-methylpropyl)-piperidine, 58%; and N-(2-amino-2-methylpropyl)-diethylamine, 20%. The diethyl derivative has not been previously reported and was characterized as follows: b. p. 87.5–89° (54 mm.); $n^{31}D$ 1.4307; d^{31}_4 0.807; mol. wt. calcd. 144.3, found 142.7; molar refrac. calcd. 46.5, found 46.3. *Anal.* N, calcd. 19.45, found 19.57.

The morpholine derivative was also obtained in 56% yield by reduction of the corresponding nitro compound by the following modification of the method of Johnson and Degering[5]: In a three-liter, three-necked flask, fitted with a condenser, a thermometer immersed in the reaction mixture, and a sealed stirrer was added 70 g. of iron powder, 150 cc. of water, 20 cc. of hydrochloric acid, 1 ml. of ferric chloride and 150 cc. of dioxane. After evolution of hydrogen ceased 62.7 g. of N-(X-nitro-2-methylpropyl)-morpholine was added with rapid stirring. The mixture was heated on a steam-bath for twenty-two hours, with stirring. To the reaction mixture was added 50 ml. of concentrated sodium hydroxide. The product was then extracted with ether and fractionated under reduced pressure after removal of the solvent.

N^1,N^4-SUBSTITUTED SULFANILAMIDES

N^1-Substituent	N^4-Acetyl Yield, %	N^4-Acetyl N Analyses, % Calcd.	N^4-Acetyl N Analyses, % Found	N^4-Acetyl M. p., °C.	N^4-Unsubstituted Yield, %	N^4-Unsubstituted N Analyses, % Calcd.	N^4-Unsubstituted N Analyses, % Found	N^4-Unsubstituted M. p., °C.
1-(4-Morpholinyl)-2-methyl-2-propyl-	92	11.82	11.50	110–113	93	13.40	13.12	213–214
1-(1-Piperidinyl)-2-methyl-2-propyl-	68	11.90	11.83	151–152	95	13.50	13.25	84–85
1-(Diethylamino)-2-methyl-2-propyl-	75	12.32	12.06	128–130	91	14.05	14.00	97–98

Preparation of N^4-Acetylsulfanilamides.—The following preparation of N^4-acetyl-N^1-[1-(diethylamino)-2-methyl-2-propyl]-sulfanilamide will illustrate the general method used in preparation of these compounds: In a flask fitted with a condenser and sealed stirrer was added 200 ml. of trichloroethylene, 11.6 g. of N^4-acetylsulfanilyl chloride (m. p. 149°) and 14.2 g. of N-(2-amino-2-methylpropyl)-diethylamine. The reaction mass was heated on a steam-bath for one hour. The product was separated from the solvent by addition of ether. It was recrystallized from 95% ethanol. The morpholine and piperidine derivatives were prepared by similar procedures.

Preparation of Sulfanilamides.—The acetyl derivatives were hydrolyzed by the following procedure: In a flask equipped with a reflux condenser was placed 3 g. of the acetyl derivative to be hydrolyzed, 30 ml. of water, 4 ml. of 40% sodium hydroxide solution, and 1 g. of sodium carbonate. The reaction mass was refluxed for six hours. The product thus formed was removed from the reaction mixture and recrystallized from 95% ethanol. The physical properties and analyses of these compounds are reported in tabular form.

Acknowledgment.—These compounds are being tested for pharmacological action by Smith,

(1) Abstracted from a thesis presented by Francis N. McMillan to the Graduate School of the University of Florida in partial fulfillment of the requirements for the M.S. degree, February, 1949.

(2) Presented before the Division of Medicinal Chemistry at the Atlantic City, N. J., meeting of the American Chemical Society, Sept., 1949.

(3) Johnson, THIS JOURNAL, **68**, 12–14 (1946).

(4) Senkus, *ibid.*, **68**, 10–12 (1946).

(5) Johnson and Degering, *ibid.*, **61**, 3194 (1939).

Kline and French Laboratories. Results of these tests will be reported elsewhere.

Summary

Three new sulfanilamide derivatives of substituted ethylenediamines have been prepared and characterized. As intermediates for these compounds, the corresponding acetyl derivatives, one new aliphatic nitroamine, and one new substituted ethylenediamine were prepared and characterized.

An improvement in the preparation of nitroamines from secondary amines, formaldehyde and 2-nitropropane is reported. A satisfactory method for reduction of aliphatic nitro compounds is reported.

GAINESVILLE, FLORIDA RECEIVED SEPTEMBER 16, 1949

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF HOPE COLLEGE]

1-Nitro-1-methylethyl Alkyl Malonic Esters

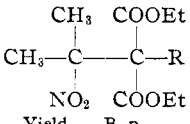
BY EUGENE E. VAN TAMELEN[1] AND GERRIT VAN ZYL

We have previously shown that, whereas 2-*bromo*-2-nitropropane reacts with sodium ethyl malonic ester to give sodium 2-nitropropane and ethyl bromomalonic ester, 2-*chloro*-2-nitropropane yields the normal alkylation product, 1-nitro-1-methylethyl ethyl malonic ester.[2] The present communication is concerned with the preparation of a series of 1-nitro-1-methylethyl alkyl malonic esters and an investigation of some of their properties.

The nitromalonic esters were obtained in fair yields by the condensation of the appropriate mono-substituted malonic esters with 2-chloro-2-nitropropane. Their properties are listed in Table I. The products are light yellow liquids, difficult to purify by the usual fractionation methods.

During the course of the initial distillation of several of these esters, white crystals identified as 2,3-dimethyl-2,3-dinitrobutane, were found to sublime. This product is also found in varying amounts while carrying out the reaction of 2-bromo-2-nitropropane and sodium ethyl malonic ester; it has its origin in the condensation of 2-bromo-2-nitropropane with the sodium 2-nitropropane formed initially.[2] The halogen interchange exhibited therein must, therefore, also be operative to some extent in the reaction of 2-chloro-2-nitropropane with mono-substituted malonic esters.

TABLE I



R	Formula	Yield, %[a]	B. p., °C.	Mm.	$n^{20}D$	Nitrogen, % Calcd.	Found
Methyl	$C_{11}H_{19}O_6N$	45	167	18	1.4483	5.36	5.20
Allyl	$C_{13}H_{21}O_6N$	46	155	6	1.4604	4.87	4.82
n-Butyl	$C_{14}H_{25}O_6N$	39	159	6	1.4511	4.62	4.86
i-Butyl	$C_{14}H_{25}O_6N$	45	151	4	1.4541	4.62	4.83
i-Amyl	$C_{15}H_{27}O_6N$	48	164	5	1.4510	4.41	4.05

[a] The yields are based on a fraction collected over a range boiling from 5° below to 5° above the b. p. of material used for analysis (adjacent column).

Catalytic reduction with Raney nickel of a typical nitro ester, 1-nitro-1-methylethyl ethyl malonic ester,[2] did not lead to the corresponding amine, but rather to a product of cleavage, ethylmalonic ester. The expected product, 1-amino-1-methylethyl ethylmalonic ester, may be considered to be the Mannich condensation product of ethylmalonic ester, ammonia and acetone; since the latter is not known to replace formaldehyde in the Mannich reaction,[3] the instability of the reduction product is not surprising. This "reverse Mannich" reaction must occur extremely readily, since considerable amounts of ammonia were evolved immediately after the completion of the hydrogenation, which was run at room temperature and at an initial pressure of 50 lb.

The nitro esters in Table I appear to be suitable for the preparation of the corresponding barbituric acids, since a typical member of the series (Table I, R = Methyl) gave the desired product, 5-(α-nitro-α-methylethyl)-5-methylbarbituric acid, upon condensation with urea in the usual manner.

Experimental[4]

1-Nitro-1-methylethyl Alkyl Malonic Esters.—The following experimental procedure was used for the preparation of the esters listed in Table I. The reactions were carried out in a 500-cc. three-necked flask equipped with a sealed stirrer and a reflux condenser (calcium chloride tube attached).

A solution of the sodium salt of the alkyl malonic ester (0.25 mole) was made ready by the addition of clean strips of sodium metal (5.7 g., 0.25 mole) to a solution of the dry ester in 225 cc. of absolute ether. The sodium reacted vigorously at first, but heating and stirring were eventually necessary to effect complete solution. The clear solution was cooled and the 2-chloro-2-nitropropane (49.2 g., 0.4 mole) added in one lot. A slight exothermic reaction usually took place, after which the contents were refluxed for seventy hours. A slight excess of glacial acetic acid was added, and then the ether solution was washed three times with 100-cc. portions of water and finally dried over sodium sulfate. Distillation from a Claisen flask yielded, after a forerun of unchanged alkyl malonic ester and other products, the desired nitro ester boiling over a 10° range. A middle cut was taken for analysis.

(1) Harvard University, Cambridge, Massachusetts.

(2) van Tamelen and Van Zyl, THIS JOURNAL, **71**, 835 (1949).

(3) Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

(4) All melting points are corrected.