Anal. Calcd. for $C_{13}H_{10}O_8N_4$: N, 16.01. Found: N, 16.5, 15.7.

3-Pyridyl Methyl Ketone Mercuric Chloride.—Forty milligrams of tobacco ketone in ethyl ether solution is added to 2 ml. of aqueous saturated $HgCl_2$ solution diluted to 6 ml. On evaporation of the ether at 5°, white needles form which are recrystallized from hot water, containing a small amount of $HgCl_2$, m.p. 161°.[35] Mixed melting points with the similarly prepared derivative of 3-pyridyl methyl ketone give no depression.

2,3'-Dipyridyl.—During the vacuum evaporation of fraction 1a, as the temperature is raised to 30° and above, a yellowish oil becomes visible at a short distance above the heated part of the evaporator. After all of the ketone has been collected, the temperature is raised to 60°. At this temperature, successive portions of condensate are collected intermittently from the condensing surfaces by rinsing with acidified water. These fractions are examined spectroscopically for homogeneity and also for estimating the yield. The absorption spectra in acid and in alkali of these fractions, shown in Fig. 3, later proved to be that of 2,3'-dipyridyl. When the evaporation becomes slower, the temperature of the bath is gradually raised to a maximum of 120° at which temperature the evaporation is continued until spectroscopic checks indicate a lack of homogeneity. At this end point, *ca.* 15% of the initial weight of fraction 1a remains as a brown tar in the evaporator.

An authentic sample of 2,3'-dipyridyl is prepared from *m*-phenanthroline[15,16] with the modification that the decarboxylation of the intermediate dicarboxylic acid is made *in vacuo*. For the preparation of derivatives, the aqueous solutions of the authentic sample as well as that of the second base of fraction 1a are extracted at *p*H 3.5, with ethyl ether.

2,3'-Dipyridyl Monostyphnate.—Thirty milligrams of tobacco dipyridyl in ether solution is added to 5 ml. of an aqueous saturated styphnic acid solution diluted to 10 ml. Yellow crystals form immediately in the ether phase, settling out as the ether evaporates. After recrystallization from hot water, a melting point of 190–191° (dec.) is obtained; a mixed m.p. with the styphnate prepared from the authentic sample of 2,3'-dipyridyl gives an identical result.

The composition of styphnate was proved by dissolving 8.2 mg. of the derivative in 2.5 *N* HCl, extracting the liberated styphnic acid with ethyl ether, transferring the latter into aqueous solution, and measuring spectrophotometrically the amounts of dipyridyl and of styphnic acid contained in the extraction residue and in the extract, respectively.

(35) C. Engler, *Ber.*, **24**, 2539 (1891), reports a m.p. of 158° for this compound.

Anal. Calcd. for dipyridyl monostyphnate: dipyridyl, 38.9; styphnic acid, 61.1. Found: dipyridyl, 37.4; styphnic acid, 62.1.

2,3'-Dipyridyl Monopicrate.—The picrate obtained by a procedure similar to that described for the styphnate, gives prior to recrystallization a dipicrate, m.p. 164°; the same result is obtained with the picrate of synthetic 2,3'-dipyridyl. Orechoff and Menschikoff[27] and Krumholz[36] report a m.p. of 166–168° for the dipicrate of 2,3'-dipyridyl. However, on repeated recrystallization of the picrates from hot water, a constant m.p. of 152° is obtained for both; mixed m.p. 152°. In agreement with the authors mentioned, these recrystallized picrates are the 2,3'-dipyridyl monopicrate:

Anal. Calcd. for $C_{16}H_{11}O_7N_5$: N, 18.2. Found: N (average of 4 determinations), 17.7.

The composition of this monopicrate is confirmed by the same procedure as described for the styphnate. Five different picrates were analyzed in this manner:

Anal. Calcd.: dipyridyl, 40.5; picric acid, 59.5. Found: dipyridyl, 40.3 ± 1.0; picric acid, 59.1 ± 1.0.

The nitrogen content of the dipyridyl was found indirectly from its picrate, using the very pure dipyridyl fraction obtained from the decomposition of the picrate:

Anal. Calcd. for $C_{10}H_8N_2$: N, 18.0. Found: N, 17.5, 17.8.

Determination of Standard Nitrogen Absorbancy[37] of Purified 2,3'-Dipyridyl.—The spectrum of the dipyridyl fraction as obtained from the vacuum evaporation apparatus agreed both in acid and in alkaline solutions with that reported by Krumholz[18] for 2,3'-dipyridyl. For a quantitative corroboration of the identity of Krumholz's and our compound, we purified the dipyridyl obtained from tobacco over its monopicrate in the manner described above and measured its absorption spectrum. The purity of the base was verified by the fact that the ratio A_{max}/A_{min} agreed within experimental limits with the value of 4.87 calculated from Krumholz's curve. Using the nitrogen content of several aliquots of this solution as found by our modified Kjeldahl procedure, the standard nitrogen absorbancy at 277 mμ of our substance was determined.

Calcd. from Krumholz's curve: 73.0. Found: 73.8, 74.8, 75.2.

(36) P. Krumholz, *Selecta Chimica*, **8**, 1 (1949).

(37) Defined as the absorbancy of a solution, containing in one liter 10 milliequivalents of the substance based on its nitrogen content.

LANCASTER, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF LIBERAL ARTS AND SCIENCES, TEMPLE UNIVERSITY]

The Preparation of a Pyrimidine Analog (Isostere) of Promizole and Other Substituted Pyrimidines

BY WILLIAM T. CALDWELL AND A. NURI SAYIN[1]

RECEIVED FEBRUARY 29, 1952

α-4-Aminophenyl-β-2-pyrimidylurea, *p*-aminophenyl-2-amino-5-pyrimidyl sulfone, 2-sulfanilamido-5-phenylmercaptopyrimidine and other 5-mercapto substituted pyrimidines have been synthesized. Pharmacological tests carried out with these compounds indicated that most of them were ineffective or but slightly active. Only a few showed activity comparable to that of sulfanilamide.

In seeking further light upon the relationship between chemical structure and physiological action it is common practice to modify certain structural features of substances of known activity in the hope of getting better correlations and guides for further investigation. In the first of the three substances whose preparation we are describing, the sulfonamide group linking the homocyclic and heterocyclic parts of sulfadiazine has been replaced by a carbamide group. In the second compound, which is an isomer of sulfadiazine, we have, instead of a sulfonamide, a sulfone which may also be looked upon as an isostere of Promizole.[2]

Particular attention may be called to the fact that in this compound and in the intermediates used in obtaining it, sulfur is directly attached in two different states of valence to position 5 of the pyrimidine nucleus. Our search of the literature

(1) Taken from a thesis submitted by A. Nuri Sayin in partial fulfillment of the requirement for the degree of Doctor of Philosophy.

(2) L. L. Bambas, U. S. Patent 2,389,126 (Nov. 20, 1945); *C. A.*, **40**, 991 (1946); THIS JOURNAL, **67**, 668 (1945).

has revealed no examples of this structural feature in pyrimidines. Mercapto derivatives with sulfur attached to other positions are common, but the only pyrimidines we have found with a sulfonyl group directly joined to the nucleus are several 2-ethylsulfonylpyrimidines[3] and 2-pyrimidinesulfonyl chloride and its amide.[4]

The third compound was made partly because of analogies of an intermediate to substances prepared as possible antitubercular agents; partly because of the results of pharmacological investigation of other 5-substituted sulfadiazines[5,6]; and partly because of the desire to introduce a mercapto group in position 5.

In introducing the latter group by our present method, we ran into some irregularities whose cause, other than general low reactivity of halogen in position 5, is not apparent to us. For example, in our hands only unchanged 5-iodo-2-aminopyrimidine and phthalimide were recovered in an experiment in which the potassium salt of the latter was heated with the former in quinoline with or without addition of dimethylformamide; the same pyrimidine was recovered unchanged after heating with the lead salt of phenyl mercaptan in quinoline at 190–200°; only a very small amount of 2-amino-5-phenylmercaptopyrimidine was formed, most of the pyrimidine being recovered; also the pyrimidine was recovered after heating it in quinoline at 180–190° with the dry potassium salt of *p*-acetamidobenzenesulfinic acid.

Unanticipated difficulty was encountered in attempting to oxidize 2-amino-5-*p*-nitrophenylmercaptopyrimidine to the sulfone. Although 2-aminopyrimidine is not oxidized even by fuming nitric acid at room temperature, 2-amino-5-*p*-nitrophenylmercaptopyrimidine (IV) was found to be very sensitive to oxidizing agents; concentrated nitric acid as well as 30% hydrogen peroxide reacted spontaneously, forming products in which the pyrimidine nucleus apparently was completely broken down. Therefore, as is usual in oxidizing sulfides containing amino groups in the para position[7] in order to obtain the desired *p*-nitrophenyl-2-amino-5-pyrimidyl sulfone (VI), it was necessary to protect by acetylation the amino group attached to the pyrimidine nucleus. Oxidation, then, of the acetylated IV was best accomplished with chromic acid in glacial acetic acid,[8] although the yield was low (20–25%). 30% hydrogen peroxide gave the same product (VI), but with even less satisfactory yield.

This oxidation of 2-acetamido-5-*p*-nitrophenylmercaptopyrimidine (VII) with chromic acid gave in addition to the desired sulfone (VI) a large quantity of yellow by-product which was separated from VI by means of its solubility in dilute ammonia. Percentage of sulfur and nitrogen indicated a sulfoxide, but confirming analysis for carbon and hydrogen failed to support this possibility. It was not further characterized beyond elementary analysis.

The reduction of the nitro group in VI was best carried out catalytically with Raney nickel in dioxane, although the time required was long—about 24 hours. Reduction with commercial ammonium sulfide[9] failed. Reduction with iron powder in a solution of 60–65% acetic acid at 85–90° for three hours yielded a different product. This, after purification and recrystallization twice from water, melted at 149–151°. Quantitative analysis for nitrogen (found: N, 14.16) led us to assume that, during reduction of the nitro group, hydrolysis of the amino group attached at position 2 in the pyrimidine nucleus took place; this followed subsequent acetylation of the amino group formed in the benzene ring. The *p*-acetamido-2-hydroxypyrimidyl sulfone (calcd.: N, 14.33) presumably thus formed, was found to be approximately as effective as sulfanilamide in *Streptococcus*, and in typhoid infected mice at 2 mg. × 2.

Finally, condensation of 2-amino-5-phenylmercaptopyrimidine (III), either with *p*-nitrophenylsulfonyl chloride, or with *p*-acetamidobenzenesulfonyl chloride in dry pyridine at 55°[10] or even under more drastic conditions, namely at 150°,[9] failed to give the desired sulfonamide. In both cases only unchanged (III) was recovered. However, 2-sulfanilamido-5-phenylmercaptopyrimidine (X) was prepared from 2-*p*-nitrophenylsulfonamido-5-iodopyrimidine[9] by replacing iodine with the phenylmercapto group according to our present procedure.

Pharmacological tests were carried out with α-4-aminophenyl-β-2-pyrimidylurea, 5-phenylmercapto-2-aminopyrimidine, 5-*p*-nitrophenylmercapto-2-aminopyrimidine, *p*-nitrophenyl-2-amino-5-pyrimidyl sulfone and 2-sulfanilamido-5-phenylmercaptopyrimidine upon mice infected with influenza virus, with *Streptococcus hemolyticus*, with *Semliki Forest* virus, and with *Meningopneumonitis* virus. These compounds were generally ineffective with the exception that *p*-nitrophenyl-2-amino-5-pyrimidyl sulfone was slightly more effective than sulfanilamide in *Streptococcus hemolyticus* and slightly effective in typhoid infected mice.

p-Aminophenyl-2-amino-5-pyrimidyl sulfone showed a slight activity *in vivo* on tuberculosis.

We wish to thank Eli Lilly and Company for carrying out the pharmacological tests, and the Temple University Committee on Research and Publications for a Grant-in-aid.

Experimental[11]

α-4-Nitrophenyl-β-2-pyrimidylurea[12] (I).—Nine grams (0.055 mole) of *p*-nitrophenyl isocyanate (Eastman Kodak Company, practical grade) was treated with 4.75 g. (0.05 mole) of 2-aminopyrimidine in 50 ml. of carbon tetrachloride

(3) T. B. Johnson and J. M. Sprague, *ibid.*, **57**, 2352 (1935); **58**, 423 (1936); **58**, 1348 (1936).

(4) R. O. Roblin, Jr., and J. W. Clapp, *ibid.*, **72**, 4890 (1950); see also Ohta and Sudo, *Chem. Abs.*, **46**, 4449 (1952); Polonovski and Schmitt, *Compt. rend.*, **232**, 2108 (1951).

(5) J. P. English, J. H. Clark, J. W. Clapp, D. Seeger and R. H. Ebel, THIS JOURNAL, **68**, 453 (1946).

(6) A. Falco, B. Russell and G. H. Hitchings, *ibid.*, **73**, 3753 (1951).

(7) E. H. Northey, "Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, p. 19.

(8) R. H. Shriner, H. C. Struck and W. J. Jorison, THIS JOURNAL, **52**, 2060 (1930).

(9) R. G. Shepherd and C. E. Fellows, *ibid.*, **70**, 159 (1948).

(10) R. O. Roblin, Jr., and P. S. Winneck, *ibid.*, **62**, 1999 (1940).

(11) All analyses were performed by Clark Microanalytical Laboratory, Urbana, Illinois. Melting points are uncorrected.

(12) R. de B. Ashworth, A. F. Crowther, F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 581 (1948); *C. A.*, **42**, 6828 (1948).

(toluene and *o*-xylene as solvents gave much lower yields). After the initial exothermic reaction, the mixture was kept at room temperature for one hour, and then refluxed for an additional hour. It was then cooled, the insoluble material filtered off, washed with hot water, dried and extracted with 1.1 liters of boiling dioxane. From this solution, upon cooling, a white precipitate separated which was practically pure; yield 5 g. or 38%. The compound after recrystallization from glacial acetic acid (100 ml./g.) melted at 274–275°.

Anal. Calcd. for $C_{11}H_9O_3N_5$: N, 27.03. Found: N, 27.16.

α-4-Aminophenyl-β-2-pyrimidylurea (II).—Four and one-half grams (0.0174 mole) of pure α-4-nitrophenyl-β-2-pyrimidylurea (I) was suspended in 90 ml. of absolute ethanol and approximately 2 g. of wet Raney nickel[13] was added. The reduction was carried out with molecular hydrogen at room temperature under 30 pounds pressure and was stopped as soon as the theoretical amount of hydrogen had been absorbed. 100 ml. of water and 50 ml. of ethanol were added and the mixture heated to dissolve all organic material. After filtering the hot solution, α-4-aminophenyl-β-2-pyrimidylurea (II) separated on cooling as white crystals; yield 3.75 g. or 94%; m.p. 212–215° (dec.). The compound was recrystallized once more from 50% ethanol for analysis.

Anal. Calcd. for $C_{11}H_{11}O_3N_5$: N, 30.56. Found: N, 30.15.

2-Amino-5-phenylmercaptopyrimidine (III).[14,15]—Eleven and four-hundredths grams (0.05 mole) of 2-amino-5-iodopyrimidine, prepared with a yield of 40–45% according to the procedure given by Shepherd and Fellows[9] was mixed with 40 ml. of quinoline (Eastman Kodak Company, practical grade). To this mixture, 9.84 g. (0.035 mole) of well dried and powdered cupric thiophenolate was added, and the mixture was then heated in an oil-bath at 190–200° for half an hour. (The cupric thiophenolate was prepared by dissolving 21 g. (0.19 mole) of thiophenol in 40 ml. of absolute ethanol, treating this alcoholic solution with 16 g. (0.08 mole) of cupric acetate monohydrate at room temperature and allowing the mixture to stand overnight. Next day, the canary-yellow precipitate formed was washed with cold ethanol, then with water, and finally dried in a vacuum desiccator.) Upon pouring the resulting dark quinoline solution into a large amount of ice-water, a precipitate separated which was removed, washed with water, and purified by solution in 3 *N* hydrochloric acid, decolorizing with charcoal, filtering, and reprecipitating with an excess of ammonia. In this way, 2-amino-5-phenylmercaptopyrimidine (III) was obtained as a white solid in a yield of 6.5 g. or 64%. The product after recrystallization from ethanol formed white needles which melted at 154–155°.

Anal. Calcd. for $C_{10}H_9N_3S$: S, 15.77. Found: S, 16.33.

2-Amino-5-*p*-nitrophenylmercaptopyrimidine (IV).—A mixture of 16.6 g. (0.075 mole) of 2-amino-5-iodopyrimidine[9] in 50 ml. of quinoline (Eastman Kodak Company) was heated to 150° and treated at this temperature with 2 g. of finely divided copper powder and 18 g. (0.093 mole) of well-dried potassium *p*-nitrothiophenolate. (This latter compound was prepared by dissolving *p*-nitrothiophenol[16] at 80–90° in 15% potassium hydroxide solution containing a little ethyl alcohol, the solution of alkali being maintained in excess. Upon cooling with ice, potassium *p*-nitrothiophenolate precipitated as brilliant red-yellow crystals.)

After heating this quinoline solution at 150–160° for 20–25 minutes, the temperature was raised to 180–190°, and kept at this temperature for an additional 20 minutes. The resulting dark-brown solution was poured into 500 ml. of boiling glacial acetic acid and filtered while still hot. The filtrate was then cooled and poured into 4–5 volumes of ice-water. The yellow precipitate formed was removed, washed with a little alcohol, then with water, and purified by dissolving in concentrated boiling acetic acid (70–80%), decolorizing with charcoal, filtering, and cooling. A yield of 13.5 g. or 73% was obtained. After recrystallization once more from 70–80% acetic acid or from acetone it melted at 204–205°; light-yellow crystals.

Anal. Calcd. for $C_{10}H_8O_2N_4S$: S, 12.91. Found: S, 12.38.

2-Amino-5-*p*-aminophenylmercaptopyrimidine (V).—Two and forty-eight hundredths grams (0.01 mole) of pure 2-amino-5-*p*-nitrophenylmercaptopyrimidine (IV) was dissolved in 50 ml. of warm dioxane (reagent grade). About 1 g. of wet Raney nickel[13] was added and the nitro group was reduced with molecular hydrogen, at room temperature, under 40 pounds of pressure. The absorption of the theoretical amount of hydrogen required approximately 24 hours of shaking. The dioxane solution was filtered off and the filtrate poured into 3–4 volumes of cold water. This precipitated completely the 2-amino-5-*p*-aminophenylmercaptopyrimidine as a yellow solid. The crude product was purified by dissolving in 15 ml. of 10% hydrochloric acid, heating with charcoal, and filtering. The free diamine was reprecipitated from the filtrate by making the solution alkaline with 10% ammonia; yield almost quantitative. After recrystallization from 50% ethanol, the product melted at 172–173°; white crystals.

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.02; H, 4.62; N, 25.67. Found: C, 54.89; H, 4.22; N, 24.90.

***p*-Nitrophenyl-2-amino-5-pyrimidyl Sulfone (VI).**—Twelve and four-tenths grams (0.05 mole) of dry, pure 2-amino-5 *p*-nitrophenylmercaptopyrimidine (IV) (m.p. 204–205°) was mixed with 3 g. of freshly fused sodium acetate. The mixture was added to 75 ml. of acetic anhydride (reagent grade) and refluxed at 160–165° for three hours. It was then cooled and poured into a large volume of ice-water whereupon the crude 2-acetamido-5-*p*-nitrophenylmercaptopyrimidine (VII) separated as a creamy-white solid. The mixture was allowed to stand approximately two hours at room temperature to ensure complete decomposition of excess acetic anhydride. The crude VII was then filtered off, washed several times with water, and dried. It was directly used for oxidation without further purification. For identification, a sample of it was recrystallized from acetone, with a considerable loss. Pure VII was a creamy-white powder melting at 220–222°.

Sixteen and two-tenths grams of chromic acid was dissolved in 15 ml. of glacial acetic acid and added dropwise to a mixture of 14 g. of dried and powdered crude VII in 170 ml. of glacial acetic acid with constant swirling. By alternate addition of reagent and cooling, the temperature was maintained close to 60° throughout the addition which was completed in about ten minutes. When the temperature began to drop spontaneously (after about 30 minutes), the solution was heated gently on a steam-bath at 85–90° for one hour to complete the oxidation. The resulting green solution was cooled to room temperature and poured into 1200 ml. of water and allowed to stand overnight to ensure complete precipitation (the sulfone separates slowly). The white precipitate was removed, washed several times with water, and heated on a steam-bath with 160 ml. of 10% hydrochloric acid for one hour. The acidic mixture was then cooled and the acid neutralized in the cold with 10% ammonia, making the solution definitely alkaline. This precipitated completely the *p*-nitrophenyl-2-amino-5-pyrimidyl sulfone (VI) as a white solid; yield 3.2 g. or 22% based on IV. The product melted after recrystallization from 70–80% acetic acid at 267–270° (dec.). Dioxane may also be used; acetone was a less satisfactory solvent.

Anal. Calcd. for $C_{10}H_8O_4N_4S$: N, 19.99. Found: N, 19.93.

The ammoniacal filtrate was acidified again with hydrochloric acid. This produced, upon standing overnight, a yellow solid which was recrystallized twice from 95% ethanol. It melted at 284–285°.

Anal. Calcd. for *p*-nitrophenyl-2-acetamido-5-pyrimidyl sulfoxide ($C_{12}H_{10}O_4N_4S$): C, 47.05; H, 3.29; N, 18.29; S, 10.47. Found: C, 41.68; H, 1.89; N, 18.26; S, 10.74.

It was not further investigated.

***p*-Aminophenyl-2-amino-5-pyrimidyl Sulfone (VIII).**—Two and eight-tenths grams (0.01 mole) of pure *p*-nitrophenyl-2-aminopyrimidyl sulfone (VI) (m.p. 267–270°) was dissolved in 150 ml. of boiling dioxane (reagent grade). After cooling the solution to room temperature, about one gram of wet Raney nickel[13] was added and the reduction

(13) H. Adkins, THIS JOURNAL, **54**, 416 (1932); "Reaction of Hydrogen with Organic Compounds," The University of Wisconsin Press, Madison, Wisconsin, 1946, pp. 19–20.

(14) J. P. English, J. H. Clark, R. G. Shepherd and others, THIS JOURNAL, **68**, 1048 (1946).

(15) H. Gilman and J. A. Beel, *ibid.*, **73**, 776 (1951).

(16) Th. Zincke and S. Lenhart, *Ann.*, **400**, 2 (1913).

was carried out with molecular hydrogen under 40 pounds of pressure, and was stopped as soon as the theoretical amount of hydrogen had been absorbed (approximately 24 hr.). The catalyst was filtered off, and the dioxane removed by distillation under reduced pressure at about 40–50°. The residue was treated with 10% hydrochloric acid, charcoal added and filtered. The filtrate was made definitely alkaline with 15% ammonia and cooled. The free *p*-aminophenyl-2-amino-5-pyrimidyl sulfone (VIII), upon standing, separated as a white solid; yield crude powder, 2.2 g. or 88%. After recrystallization from water, the product melted at 207–208°; white, microscopic needles.

Anal. Calcd. for $C_{10}H_{10}O_2N_4S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 48.37; H, 4.09; N, 22.41.

2-Sulfanilamido-5-phenylmercaptopyrimidine (X).—2-*p*-Nitrophenylsulfonamido-5-iodopyrimidine was prepared from 2-*p*-nitrophenylsulfonamidopyrimidine with a yield of 65–70% according to the method given by Shepherd and Fellows[3] for direct iodination of phenylsulfonamido heterocycles.

Eight and twelve-hundredths grams (0.02 mole) of pure and dry 2-*p*-nitrophenylsulfonamido-5-iodopyrimidine (m.p. 288–290°) was mixed with 50 ml. of quinoline (Eastman Kodak Company, practical grade). To this 4.22 g. (0.015 mole) of cupric thiophenolate was added and the mixture was then heated in an oil-bath at 180–190° for 30 minutes. Upon pouring the resulting dark solution into 200 ml. of 70–80% acetic acid and cooling, a precipitate separated which was filtered and washed with water. The precipitate was treated with 10% ammonia (10 ml./g.), charcoal added, filtered and to the filtrate an equal volume of 5 *N* sodium hydroxide solution was added. The sodium salt of 2-*p*-nitrophenylsulfonamido-5-phenylmercaptopyrimidine (IX) separated upon cooling. It was filtered off and washed with aqueous alkali. After solution in warm 20% alcohol, the free IX was precipitated by acidification with 30% acetic acid; yield 4.5 g. or 58%. The product after recrystallization from 95% ethanol melted at 223–224°; light yellow, fine crystals.

Three and eighty-eight hundredths grams (0.01 mole) of IX was boiled with 80 ml. of commercial ammonium sulfide solution for 5 minutes. The resulting red-brown mixture was added to a large amount of 60% acetic acid, and the solid formed was purified by solution in 50 ml. of 10% ammonia solution, heating with charcoal and filtering. The filtrate was poured into 50 ml. of 5 *N* sodium hydroxide solution and cooled. This caused separation of the sodium salt of X as a white solid, which was filtered and washed with aqueous alkali. The precipitate was dissolved in warm 20% alcohol and X was reprecipitated by acidification with 30% acetic acid. The yield was 2.8 g. or 78%. The product after recrystallization from 95% ethanol melted at 217–218°; white brilliant crystals.

Anal. Calcd. for $C_{16}H_{14}O_2N_4S_2$: N, 15.63. Found: N, 15.11.

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Derivatives of 2,2-Dimethylethylenimine

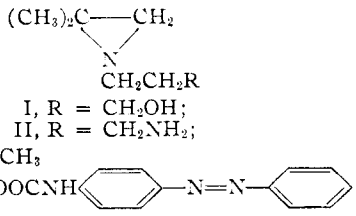
BY HENRY M. KISSMAN[1] AND D. S. TARBELL

RECEIVED MARCH 12, 1952

The urethan (XVI) derived from 2,2-dimethyl-1-(γ-hydroxypropyl)-ethylenimine and 4-(*p*-*d*-camphorsulfonylamino)-phenylazonaphthyl isocyanate was synthesized in an attempt to prepare optically active intermediates for the resolution of ethylenimine derivatives. The syntheses of two other optically active isocyanates are discussed.

This paper describes experiments carried out in continuation of work designed to test the resolvability of the trivalent nitrogen atom in 2,2-dimethylethylenimine.[2]

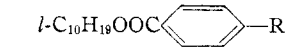
2,2-Dimethyl-1-(γ-hydroxypropyl)-ethylenimine (I), the amino analog (II) of which was reported previously,[2b] has been prepared by two methods. The first was the addition of 2,2-dimethylethylenimine to allyl alcohol in the presence of sodium allyloxide[3]; the second, and more satisfactory, method was the lithium aluminum hydride reduction of 2,2-dimethyl-1-(β-carbomethoxymethyl)-ethylenimine (III), which was prepared by the addition of 2,2-dimethylethylenimine to methyl acrylate.



I, R = CH_2OH;
II, R = CH_2NH_2;
III, R = $COOCH_3$
IV, R = CH_2OOCNH–C$_6$H$_4$–N=N–C$_6$H$_5$

A colored urethan IV was prepared from the alcohol (I) and *p*-phenylazophenyl isocyanate,[4] with the object of resolving it by adsorption on lactose following Prelog's elegant method for resolving Troeger's Base[5]; this was unsuccessful, due probably to lack of proper surface activity of the lactose.

The other derivatives of I and II were prepared from optically active reagents with the object of separating the resulting diastereoisomers by crystallization or chromatography,[6] and thus demonstrating the existence of asymmetry due to the trivalent nitrogen atom. The urethan and urea derivatives prepared from I and II and *l*-α-phenylethyl isocyanate[2a] were non-crystalline, as were also those from the isocyanate (V) derived from *l*-menthyl *p*-aminobenzoate (VI). This isocyanate was prepared from the ester V with phosgene and was characterized as the crystalline piperidine derivative VII.



V, R = NCO
VI, R = NH_2
VII, R = $NHCONC_5H_{10}$

The synthesis of a colored optically active isocyanate was undertaken, using the *l*-menthoxyacetyl derivative of 4-amino-2-methyl-4′-nitroazobenzene (VIII) as starting material. However,

(1) Beaunit Mills Fellow, 1949–1950.

(2) Previous papers: (a) T. L. Cairns, THIS JOURNAL, **63**, 871 (1941); (b) D. S. Tarbell and D. K. Fukushima, *ibid.*, **68**, 2499 (1946).

(3) *Cf.* O. Hromatka, *Ber.*, **75**, 131, 379 (1942); A. W. Weston, U. S. Patent 2,437,984 (*C. A.*, **42**, 4605 (1948)).

(4) L. C. Raiford and H. B. Freyermuth, *J. Org. Chem.*, **8**, 230 (1943).

(5) V. Prelog and P. Wieland, *Helv. Chim. Acta*, **27**, 1127 (1944).

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