TABLE I

2-AMINOPYRIMIDINE-5-SULFONAMIDE AND SOME OF ITS N^1,N^4-DISUBSTITUTED DERIVATIVES[a]

Reagent	M.p., °C.	Crystn. solvent	Yield, %	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ammonia	283–285	Water	48.3	$C_4H_6N_4O_2S$	27.58	27.61	3.47	3.51	32.17	31.93
Methylamine	194–195	Water	90.5	$C_6H_{10}N_4O_2S$	35.63	35.72	4.98	5.03	27.71	27.41
Dimethylamine	200–201	Ethanol–water	86.5	$C_8H_{14}N_4O_2S$	41.72	41.94	6.13	6.22	24.33	24.14
Ethylamine	191–192	2-Propanol–water	58.5	$C_8H_{14}N_4O_2S$	41.72	41.58	6.13	6.20	24.33	24.30
Diethylamine	72–73	Ethanol–water	83.2	$C_{12}H_{22}N_4O_2S$	50.32	50.37	7.74	7.66		
n-Propylamine	162–163	2-Propanol–water	82.3	$C_{10}H_{18}N_4O_2S$	46.49	46.55	7.02	7.02	21.69	21.69
n-Butylamine	165–167	Ethanol–water	80.5	$C_{12}H_{22}N_4O_2S$	50.32	50.39	7.74	7.64	19.57	19.46
Allylamine	165–167	Ethanol–water	88.4	$C_{10}H_{14}N_4O_2S$	47.23	47.11	5.55	5.54	22.03	22.03
Cyclohexylamine	156–158	2-Propanol–water	90.2	$C_{16}H_{26}N_4O_2S$	56.77	56.85	7.74	7.88	16.55	16.65
Pyrrolidine	215–217	2-Propanol–water	85.1	$C_{12}H_{18}N_4O_2S$	51.04	50.94	6.43	6.44	19.84	19.84
N-Methylpiperazine	180–182	Water	83.5	$C_{14}H_{24}N_6O_2S$	49.39	49.34	7.11	7.23	24.69	24.72
Morpholine	223–224	2-Propanol–water	78.3	$C_{12}H_{18}N_4O_4S$	45.85	46.09	5.77	5.88	17.82	17.76
Piperidine	199–200	2-Propanol–water	81.4	$C_{14}H_{22}N_4O_2S$	54.14	54.06	7.14	7.26	18.05	18.12

[a] Prepared from 2-chloro-5-pyrimidinesulfonyl chloride with the reagents listed in column 1 under the same conditions as described for the reaction with methylamine.

of 4.8 g. (0.05 mole) of ammonium carbonate was heated at 100° for three hours. After cooling, the contents of the flask were poured into 25 ml. of water, the precipitate filtered off and recrystallized from water; yield of white needles, 0.84 g. (48%), m.p. 283–285°. The same product is obtained from the chloride by using concentrated ammonium hydroxide or a solution of dry ammonia in tetrahydrofurane.

Anal. Calcd. for $C_4H_6N_4O_2S$: C, 27.58; H, 3.47; N, 32.17. Found: C, 27.61; H, 3.51; N, 31.93, 32.49.

2-Methylamino-5-pyrimidine-N-methylsulfonamide.—Two grams of methylamine was bubbled into 50 ml. of cooled benzene and then 2.13 g. (0.01 mole) of 2-chloro-5-pyrimidinesulfonyl chloride in 50 ml. of benzene was added with stirring during a period of 15 minutes. After stirring for an additional 15 minutes, the white product was filtered off and washed with water to remove methylamine hydrochloride. Crystallization from water afforded 1.83 g. (90.5%) of white crystals, m.p. 194–195°.

Anal. Calcd. for $C_6H_{10}N_4O_2S$: C, 35.63; H, 4.98; N, 27.71. Found: C, 35.72; H, 5.03; N, 27.41.

2-Amino-5-pyrimidinesulfonic Acid.—Forty-seven and one-half grams (0.5 mole) of finely powdered 2-aminopyrimidine was added very slowly with vigorous stirring to 300 ml. of chlorosulfonic acid cooled in a bath of ice and salt to 10°. After all of the 2-aminopyrimidine had been added, the mixture was refluxed for 8 hours, cooled and poured carefully upon crushed ice. After standing overnight in a refrigerator the solid was filtered off, washed well with cold water and recrystallized from water. The yield of white crystals, m.p. 305–307° dec., was 22.8 g. (28%).

Anal. Calcd. for $C_4H_5N_3O_3S$: C, 27.42; H, 2.88; N, 24.00. Found: C, 27.82; H, 3.03; N, 24.02.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND THE ENGINEERING EXPERIMENT STATION, GEORGIA INSTITUTE OF TECHNOLOGY]

Spiroaminobarbituric Acids. I[1]

BY JAMES A. STANFIELD AND PHILLIP M. DAUGHERTY

RECEIVED OCTOBER 2, 1958

The synthesis of several nitrogen-substituted alkyl, substituted alkyl and aryl derivatives of spiropiperidine-4′,5-barbituric acid is reported. It has been observed that the stability of the spiro-1′-methylpiperidine-4′,5-barbituric acid is of the same order of magnitude as barbital and is somewhat more stable than the spirotetrahydropyran- or the spirocyclopentanebarbituric acids. The pharmacological examinations of the 1′-phenyl- and the 1′-(2-phenylethyl)- compounds are also reported.

Cyclic diimides, prepared by condensing urea or its derivatives with various substituted malonic esters, form an important group of compounds many of which have a depressant action on the central nervous system. Such compounds, the barbiturates, are valuable sedatives and soporifics. Among these, the most useful are those compounds having two substituents, usually alkyl, at the number 5 position. Close analogs of these, the spirobarbiturates, many of which incorporated a spirocarbocyclic system involving the 5-position, have been prepared by previous investigators in the field.[2] The most recent effort along these lines, however, was the preparation of a spironitrogen system, *i.e.*, spiro-1′-benzenesulfonylpiperidine-4′,-5-barbituric acid.[3] This present work reports the preparation of several spiro-1′-alkyl- or arylpiperidine-4′,5-barbituric acids, two possible approaches to the synthesis of compounds of this type being outlined in Figs. 1 and 2.

(1) A portion of this material was presented at the 130th Meeting of the American Chemical Society in Atlantic City, N. J., September, 1956, and is taken in part from the Ph.D. thesis submitted to the Graduate School of the Georgia Institute of Technology by Phillip M. Daugherty in May, 1957.

(2) (a) A. W. Dox and L. Yoder, THIS JOURNAL, **43**, 677 (1921); (b) **43**, 1366 (1921); (c) O. Kamm and J. H. Waldo, *ibid.*, **43**, 2223 (1921); (d) A. C. Cope, P. Kovacic and M. Burg, *ibid.*, **71**, 3658 (1949); (e) W. J. Doran and E. M. Van Heyningen, U. S. Patents 2,561,688 and 2,561,689 (July, 1951); (f) J. Buchi, K. Leuenberger and R. Lieberherr, *Farm. Sci. e tec.* (*Pavia*), **6**, 430 (1951); and (g) G. Giacomello and P. Malatesta, *ibid.*, **6**, 684 (1951).

(3) G. S. Skinner, H. R. Krysiak and J. A. Perregrino, THIS JOURNAL, **77**, 2248 (1955).

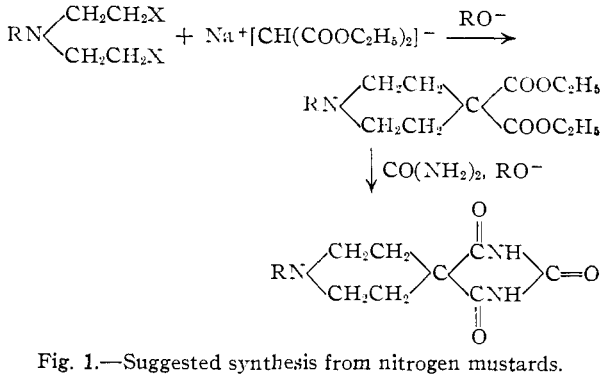


Fig. 1.—Suggested synthesis from nitrogen mustards.

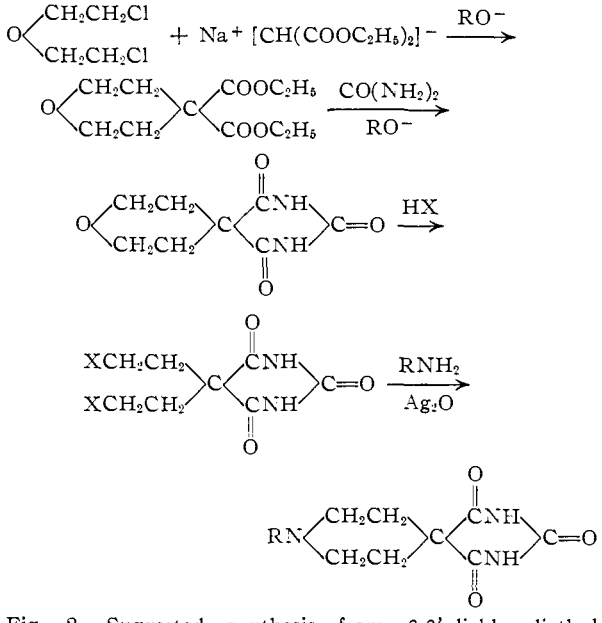


Fig. 2.—Suggested synthesis from β,β'-dichlorodiethyl ether.

The more direct route as outlined in Fig. 1 is comparable to that generally used in the preparation of alkyl substituted barbiturates. Similar reactions using β,β'-dichlorodiethyl ether instead of the nitrogen mustards are quite well known.[4] The use of nitrogen mustards in the formation of 4,4-disubstituted piperidine derivatives is less well known, although the formation of 1-phenyl-4,4-dicarbethoxypiperidine by this method has been reported.[5] The condensation of nitrogen mustards with arylacetonitriles to form Demerol and related compounds is also known.[6] In spite of these reported condensations, we have not experienced much success with the condensation of alkyl or unsubstituted nitrogen mustards with malonic ester. While the dihaloamine apparently did react with diethyl malonate (as evidenced by the almost immediate precipitation of sodium halide upon addition of the amine to the sodiomalonic ester), poor yields, usually less than 10%, were obtained from the reaction mixture. This, plus the rather potent vesicant action of these compounds, both as free bases and as the hydrochloride salts, seemed to render this reaction path less desirable, although continued work is underway with this sequence.

Figure 2 illustrates the successful synthesis of the spironitrogen systems. Kamm and Waldo[2c] succeeded, in 1921, in preparing the spirotetrahydropyranbarbituric acid. Duplication of this work indicated the method of isolation of the free acid from the mixture of sodium salts of the reaction mixture to be sensitive to slight variations in procedure. In cases wherein aqueous hydrochloric acid was used, whether maintaining the reaction mixture at room temperature or at 0°, lower yields of the free acid were consistently obtained. The decrease in yields resulted primarily from the hydrolysis of the barbituric acid. This is well illustrated by the isolation of not only tetrahydropyran-4-carboxy-4-carbonylureide, but also a slight amount of the tetrahydropyran-4-carbonylureide from the crude precipitated barbituric acid. In fact, when the sodium salts (I) of the original reaction mixture were dissolved in cold water and then acidified at 0°, a 25% yield of carboxyureide II could be obtained. This could be decarboxylated easily by heating in vacuum to form the ureide III. Even upon standing 24 hours in sodium hydroxide, compound II gave rise to tetrahydropyran-4,4-dicarboxylic acid when the solution was acidified. This compound, IV, was easily converted by heating at its melting point to the mono acid V. Thus, the ease of basic hydrolysis seems to account quite adequately for low yields of product if aqueous conditions are involved. A similar situation has been indicated with a C_5-spirobarbituric acid.[7]

Both the pyran and pyrimidine ring systems of spirotetrahydropyranbarbituric acid were found to be reasonably stable in acid media. Attempts to cleave the pyran system using aqueous hydrobromic acid solutions were ineffective. The use of 96% phosphoric acid and potassium iodide was satisfactory and gave good yields of a product in which only the pyran ring was cleaved.

In basic solution, the spiro-1'-methylpiperidine barbituric acid appears to be considerably more stable than the spiropyran acid. Kinetic experiments using 10^{-4} molar solutions of 5,5'-diethyl-(barbital), spirocyclopentane-, spirotetrahydropyran-, and spiro-1'-methylpiperidine-barbituric acids in 0.95 *N* sodium hydroxide indicated the spiropiperidine derivative to be only slightly less stable than the barbital, and considerably more stable (by a factor of the order of 10^3) than the spirotetrahydropyran compound at the reaction temperature of 40°. The spiropyran derivative was found to cleave about twice as fast as the spirocyclopentane materials.[8] Further studies on the relative stabilities of the spiropiperidine barbituric acids will be reported in a later paper.

The condensation of the 5,5-bis-(2-iodoethyl)-

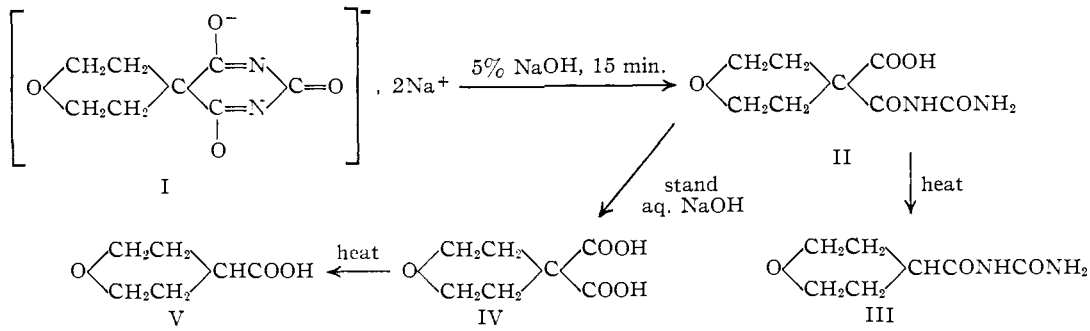
(4) (a) G. S. Skinner, THIS JOURNAL., **47**, 1124 (1925); (b) F. H. Harnest and A. Burger, *ibid.*, **65**, 370 (1943).

(5) R. M. Anker, A. H. Cook and I. M. Heilbron, *J. Chem. Soc.*, 917 (1945).

(6) O. Eisleb, *Ber.*, **74B**, 1433 (1941); O. Eisleb, U. S. Patent 2,167,351 (July, 1939).

(7) G. S. Skinner, G. Limperos and R. H. Pettibone, THIS JOURNAL., **72**, 1648 (1950).

(8) Skinner and co-workers (refs. 3 and 7) have indicated that the pyrimidine ring in both spirocyclopentanebarbituric acid and spiro-1,-benzenesulfonylpiperidine-4',5-barbituric acid are easily cleaved by aqueous alkali. No quantitative comparison is given, however.



I II III IV V

barbituric acid with various aryl and alkyl amines to form the spiro compound was found to require rather mild reaction conditions. Reactions attempted at temperatures of 60–100° led to the formation of tars and oils from which no identifiable products could be isolated, but at lower temperatures good yields resulted.

Spirobarbituric acids have not, in general, shown much promise as sedatives. Two of the compounds prepared in this work, the 2-phenylethyl- and the phenyl-derivatives were screened for possible sedative, hynotic and anticonvulsant action.[9] Neither of the compounds possessed any sedative or hypnotic action when administered intraperitoneally in a dose of 500 mg./kg. to white rats. While being mildly to moderately irritating to the test animals, no deaths occurred at this dosage level. The anti-convulsant action of these two compounds and phenobarbital was tested against Metrazol. The results of these tests indicated that these compounds neither delayed nor prevented the onset of convulsions.

Experimental[10]

Thionyl Chloride.—Distillation Products' practical grade thionyl chloride was purified by treatment with sulfur according to the procedure of Cottle.[11]

Bis-(2-chloroethyl)-methylamine hydrochloride was prepared in the conventional manner from methyldiethanolamine hydrochloride and thionyl chloride. The salt, after recrystallization from dry acetone, melted at 111–112° (uncor.).

Bis-(2-chloroethyl)-methylamine.—The free base was obtained from the hydrochloride by making a water solution of the salt basic with 20% sodium hydroxide. From the organic layer a fraction boiling at 60–70° at 2–4 mm. was obtained and used in subsequent condensations.

Diethyl 1-Methylpiperidine-4,4-dicarboxylate.—To 11.5 g. (0.5 g. at.) of sodium dissolved in 200 ml. of absolute ethanol was added 80.1 g. (0.5 mole) of diethyl malonate. When the mixture had been stirred a short time, 52.0 g. (0.33 mole) of bis-(2-chloroethyl)-methylamine was added slowly. Sodium chloride began to precipitate almost at once. After refluxing overnight another 11.5 g. of sodium in 200 ml. of absolute ethanol was added and then 26 g. more of the amine. At the termination of a reflux period of 20 hours, the liquid portion was decanted and the salt residue washed thoroughly with several portions of ethanol. The liquid portions were combined with the original filtrate, and subjected to distillation to remove the ethanol. The resulting amber-colored liquid was washed with 50 ml. of cold water and extracted three times with 50-ml. portions of ether. Combining the extracts, drying over sodium hydroxide, and distilling the ether, gave a residual oil which was fractionated at 6–7 mm. to give 7.5 g. of a pale yellow liquid boiling at 128–133°. The product gave positive tests for ester and nitrogen, and evolved a basic gas when fused with sodium.

Attempted condensation of this ester with urea in dry isopropyl alcohol–sodium isopropoxide failed to yield any identifiable material. A small quantity of an unidentified tan solid, melting with decomposition at 210–215°, was the only isolatable material.

Diethyl Tetrahydropyran-4,4-dicarboxylate.—Using the method of Harnest and Burger,[4b] a 52% yield of this ester was obtained. The boiling point of the material was 91–95° at 2.5 mm., 100–105° at 3.5 mm. or 128–132° at 9.5 mm. Saponification of the ester followed by acidification of the alkaline reaction mixture yielded the known diacid (m.p. 172–173° uncor.). Upon heating of this diacid at the melting point, decarboxylation occurred and the known tetrahydropyran-4-carboxylic acid was obtained. It melted at 86.5–87° (uncor.).

Mixing 1.5 g. of the diester with 20 ml. of concentrated ammonium hydroxide, letting the mixture stand for four days at 30° and then removing the excess ammonium hydroxide, there was obtained an almost quantitative yield of the previously unreported diamide. The melting point was 156.5–157°.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.85; H, 7.03; N, 16.28. Found: C, 48.76; H, 6.94; N, 16.15.

Ethyl tetrahydropyran-4-carboxylic acid-4-carboxylate was prepared from the diester by adapting the method of Smith.[12] The half-ester, obtained as white needles from water, melted at 97–98°.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.97. Found: C, 53.38; H, 6.89.

Spirotetrahydropyran-4',5-barbituric Acid.—Small pieces of sodium (46 g., 2 g. at.) were added to two liters of isopropyl alcohol, and, after all had reacted, 126 g. of urea and then 460 g. of diethyl tetrahydropyran-4,4-dicarboxylate was added. The mixture was refluxed gently and was stirred with a sturdy, efficient stirrer for a period of four hours during which time it became quite thick and pasty. The whole was then cooled to about 5° and dry hydrogen chloride passed in slowly so that the temperature could be maintained below 10°. Stirring was continued the entire time. When the material became fluid and tested acid to litmus, the gas flow was stopped. The solids were separated by centrifugation and transferred to a vacuum system where, under aspirator pressure, some of the excess hydrogen chloride was removed. The solid was washed well with cold (5°) water and collected by filtration. The yield of dried material was 200 g. This was recrystallized from three liters of isopropyl alcohol–water mixture (ratio 1:5) to give 180 g. of solid melting at 219–220°. Evaporation of the centrifugate to a small volume at reduced pressure and then addition of 500 ml. of cold water gave an oily material, which after drying and fractionating at 0.5 mm. gave 90 g. of unreacted ester. Based on the actual amount of ester consumed during the reaction, the yield of purified monohydrate barbituric acid was 52.5%.

In variations of the method of isolation of barbituric acid, the alcohol-moist sodium salts were added to a mixture of concentrated hydrochloric acid (in large excess) and ice. The whole was shaken vigorously at 0°, but only a 15% yield of free barbituric acid was obtained. In another experiment it was noted that if the amount of hydrochloric acid was only on the order of 0.5 mole excess, the yield of barbituric acid obtained was 35%. On the other hand, a solution of the sodium salts in water followed by acidification with

(9) The pharmacological testing was carried out by Scientific Associates, St. Louis, Mo.

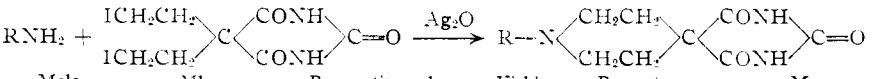
(10) All melting points, unless indicated, are corrected. Microanalyses were made by the Geller Microanalytical Laboratories, Hackensack, N. J.

(11) D. L. Cottle, THIS JOURNAL, **68**, 1381 (1946).

(12) E. L. Smith, *J. Chem. Soc.*, 1289 (1927).

TABLE I

SPIROPIPERIDINEBARBITURIC ACIDS[a]



R	Mole reactants	Ml. solvent	Reacn. times, hr. Initial	1st	2nd	Yield, %	Recrystn. solvent	M.p., °C.[b]	Nitrogen, % Calcd.	Found[c]
Methyl	0.0109	100 ethanol	1.0	0.5	1	61	Acetone	160–160.5	19.89	20.07
Ethyl	.05	350 ethanol	1.75	10	10	85	Ethanol	166–167	18.66	18.84
2-Hydroxyethyl	.05	350 methanol	3.0	10	10	29	Methanol	277–278	17.42	17.46
Allyl	.02	100 methanol	1.25	2	3	38	Acetone	134.5–135	17.71	17.85
Isopropyl	.05	350 methanol	3.0	16	40	55	Acetone	143–145	17.49	17.42
n-Butyl	.02	100 methanol	1.0	48	1	30	Methanol–ether	174–175	16.59	16.66
Cyclohexyl	.05	350 methanol	1.0	10	10	64	Ethanol	194–196	15.01	14.96
Phenyl	.02	100 methanol	1.0	1.5	48	55	Water	202–202.5	15.38	15.18
Benzyl	.02	100 ethanol	1.0	45	1	45	Ethanol	173–174	14.63	14.61
o-Tolyl	.05	175 methanol	8.0	96	72	29	Methanol	178–179	14.63	14.30
p-Tolyl	.025	175 ethanol	8.0	8	24	53	1-Butanol	157–158	14.63	14.68
2-Phenylethyl	.05	300 ethanol	8.0	2	4	58	Ethanol	185–187	13.94	13.75

[a] Infrared spectra of each of the compounds were obtained using the Perkin–Elmer model 21 infrared spectrophotometer. Pellets were prepared from 0.001 g. of the compound and 0.099 g. of potassium bromide With the exception of the 2-hydroxyethyl compound, strong absorptions were observed within ±0.05 μ of 3.25, 5.80, 6.00, 8.05 and 9.50 μ. The 2-hydroxy compound showed strong absorptions at 3.29, 6.10, 6.43, 7.07, 9.43 and 9.58 μ. In addition to these, each of the compounds showed other bands particularly in the region of 6.75–9.0 μ. [b] All melting points are corrected and determined using a Kofler hot-stage micro melting point apparatus. The compounds melted with slight decomposition and were usually introduced into the apparatus within a few degrees of the expected melting point. [c] Analyses by the Geller Microanalytical Laboratories, Hackensack, N. J.

hydrochloric acid at 0° gave little of the spiroacid, but rather a 25% yield of crude tetrahydropyran-4-carboxy-4-carbonylureide which melted at 234–235°. Recrystallization from isopropyl alcohol yielded the pure material, m.p. 236–236.5° (uncor.).

Anal. Calcd. for $C_8H_{12}N_2O_5$: N, 12.96; neut. equiv., 216. Found: N, 12.84; neut. equiv., 209.

When heated to 88° under a vacuum of 2 mm., the above sample lost carbon dioxide. Recrystallization of the residue from isopropyl alcohol gave a non-acidic white solid melting at 239.5-2409 (uncor.). This was the tetrahydropyran-4-carbonylureide.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.97; H, 6.97; N, 16.29.

Hydrolysis of this ureide, effected by refluxing in 0.5 *M* sodium hydroxide, yielded the sodium salt of the known tetrahydropyran-4-carboxylic acid from which the free acid was obtained in the usual manner.

Stability of Spirotetrahydropyran-4′,5-barbituric Acid in Basic Medium.—A solution of 1.0 g. of the barbituric acid in 10 ml. of sodium hydroxide solution containing 0.5 g. of the base was allowed to stand at room temperature for 15 minutes and then acidified with hydrochloric acid. A white solid, which began to melt at 217° with the evolution of an odorless gas, was obtained. It appeared that the solid was the impure carboxy-ureide mentioned above, since, upon redissolving the material in sodium hydroxide solution and letting it stand for 24 hours at room temperature, tetrahydropyran-4,4-dicarboxylic acid (m.p. 173–174° with gas evolution) was obtained when the solution was acidified. The melt, after solidifying, remelted at 87°. A mixed melting point with an authentic sample of the tetrahydropyran-4-carboxylic acid gave no depression.

Stability of Spirotetrahydropyran-4′,5-barbituric Acid in Acidic Medium.—A 1.0-g. sample of the hydrated barbituric acid was heated 75 minutes on a steam-bath with 5 ml. of concentrated sulfuric acid. The solution became light brown in color and, when poured into a mixture of ice and water, yielded white needles. Recrystallization once from water gave 0.7 g. of the original compound. No other product was isolated.

5,5-Bis-(2-iodoethyl)-barbituric Acid.—A mixture of 200 g. of 96% phosphoric acid (prepared from 85% acid and phosphorus pentoxide), 100 g. of potassium iodide and 43.2 g. of spirotetrahydropyran-4′,5-barbituric acid (monohydrate) was shaken vigorously for 10 hours at a temperature of 135°. While warm, the resulting dark solution was poured onto 400 g. of crushed ice and the yellow solid which separated was removed by filtering and washed well with cold water. The yield of crude material which melted at 205–208° was 75% of theoretical. Washing with hot (60°) water removed the unreacted starting material from the product and recrystallization from a dioxane–water mixture gave the pure product, melting with decomposition at 207–208°.

Anal. Calcd. for $C_8H_{10}N_2O_3I_2$: C, 22.04; H, 2.27; N, 6.44; I, 58.2. Found: C, 22.05; H, 2.31; N, 6.42; I, 58.0.

Other attempts to prepare the above compound were unsuccessful; thus, aqueous hydriodic acid (sp. gr. 1.5) either at room temperature for 40 hours or at 80° for one hour failed to yield any of the di-iodo compound.

Attempts to prepare the corresponding di-bromo compound also were not successful. In these trials, 30% hydrobromic acid in acetic acid at room temperature for 40 hours, 48% hydrobromic acid containing a small amount of concentrated sulfuric acid at 110° for 20 hours and 96% phosphoric acid and sodium bromide shaken at 150° for 10 hours, all were found ineffective. In the first case only starting material was recovered, and in the other two instances only tars and a red oil resulted.

Spiro-piperidinebarbituric Acids.—A summary of the methods of preparation and the properties of these compounds is given in Table I. In general, the bis-iodoethylbarbituric acid was suspended in the prescribed amount of an absolute alcohol and then the amine was added. The amine was introduced usually in an alcoholic solution containing 10 g. of the amine in 100 ml. of solution. The mixture was placed in a glass-stoppered bottle, wrapped so as to exclude light, and then shaken mechanically for a short period of time. During this interval, two mole equivalents of silver oxide was prepared by adding a slight excess of 20% sodium hydroxide solution to a weighed amount of silver nitrate dissolved in water. The silver oxide which precipitated was removed by filtration and washed free of sodium hydroxide with cold water. Washing the oxide with several portions of absolute ethanol removed most of the water. At the end of the first interval of time, half of this silver oxide was added to the reaction mixture and shaking was continued for the time indicated in Table I by the column marked "1st." The remainder of the silver oxide then was added. Shaking now was continued for the period of time indicated by the column marked "2nd," and, at the conclusion of this final period, the reaction mixture was warmed to 65° and filtered. The collected solid was extracted thoroughly with warm absolute alcohol. In the case of the phenyl compound, dioxane was necessary to remove all the spiro-compound from the solid. From the combined extracts and original reaction mixture the spiro-compound was isolated. For the methyl, ethyl, isopropyl and cyclohexyl compounds,

this was achieved by cooling thoroughly the combined solutions. Upon addition of an excess of cold ether, the product precipitated and could be collected and recrystallized. The other compounds listed in Table I were isolated more readily by evaporation of the washes and reaction mixtures under reduced pressures until either a solid or gummy mass resulted. This solid or gum was then recrystallized from the appropriate solvent. Decolorizing charcoal was used in those cases where the solid or gum was highly colored.

Acknowledgment.—The authors wish to express their appreciation to the Public Health Service, National Institutes of Health, for a research grant, B-889, under which much of this work was carried out.

ATLANTA 13, GA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Relative Rates of Inversion and C1 Acetoxy Exchange During Anomerizations of Acetylated Aldopyranoses[1]

BY WILLIAM A. BONNER

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A series of C1 acetoxy labeled acetylated aldopyranose anomers including hexoses, 6-deoxyhexoses and a pentose has been prepared. Each substance in the series has been subjected at 25° to an anomerizing environment consisting of 1:1 acetic anhydride–acetic acid solvent containing sulfuric acid catalyst, and the rate of the resulting loss of the C1 acetoxy label for each anomer has been compared to its polarimetrically determined inversion rate. It has been found that those acetylated aldopyranose anomers having a *cis* relationship of acetoxy groups at C1–C2 show C1 acetoxy exchange rates identical within experimental error to their inversion rates, regardless of the epimeric configuration at C2 or the nature of the substitution at C6. Acetylated aldopyranose anomers having a *trans* relationship of acetoxy groups at C1–C2, on the other hand, display C1 acetoxy exchange rates 3 (for acetylated pentoses) to 14 (for acetylated hexoses) times as great as their corresponding inversion rates. These observations are amenable to two mechanistic interpretations: (1) the fundamental mechanism for anomerization is an SN2 displacement, accounting for the identical inversion and C1 acetoxy exchange rates for *cis*-C1–C2 acetylated aldopyranoses; the enhanced C1 acetoxy exchange rate for *trans*-C1–C2 anomers is then rationalizable on the basis of competing neighboring group participation by the *trans*-C2 acetoxy group. (2) The mechanism for anomerization is an SN1 ionization producing a hybrid carbonium ion capable of reacting with its anomerizing environment to yield products of both retained and inverted configuration. The present data permit no distinction between these mechanistic alternatives.

Introduction

When an acetylated aldopyranose is dissolved in a mixture of acetic anhydride and acetic acid containing a Lewis acid catalyst, it undergoes more or less rapid conversion to an equilibrium mixture of its anomers (the α-form usually predominating), a process which has had considerable preparative utility in the past.[2] This anomerization reaction has been studied from a fundamental viewpoint by several investigators[3-7] with the discovery of the following generalizations concerning it: (1) the rate of anomerization is first order with respect to acetylated aldopyranose and very nearly first order in acid catalyst,[3,4,7] that is, for the process

$$\alpha\text{-anomer} \underset{k\beta}{\overset{k\alpha}{\rightleftharpoons}} \beta\text{-anomer}$$

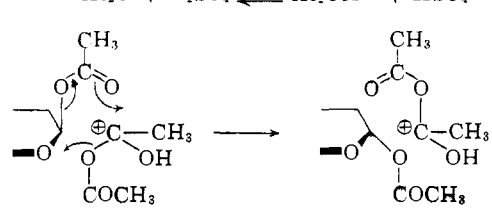
the rate data are expressed quite adequately by the relationship

$$\text{rate} = (k_\alpha + k_\beta)[\text{acid catalyst}][\text{acetylated aldopyranose}] \quad (1)$$

(2) The anomerization reaction is specific for the anomeric center and does not involve inversion[3,5] or acetoxy exchange[6,8,9] at any carbon other than C1 in the acetylated aldopyranose ring. (3) Anomerization does not appear to be subject to any primary salt effect.[3] (4) The rate of anomerization is greatest in pure acetic anhydride solvent, diminishing in a predictable fashion[3] as the acetic anhydride is diluted with acetic acid[3,4] (or butyl ether[3]), and reaching a minimum value in pure acetic acid.[3,4] (5) The products of anomerization and the positions of anomerization equilibria are independent of the acetic anhydride–acetic acid ratio in the anomerization solvents.[3,4] (6) The kinetic features of the anomerization reaction are similar among a broad series of acetylated aldohexoses and aldopentoses.[7] (7) Acetylated aldopentoses undergo anomerization significantly more rapidly than do acetylated aldohexoses.[7] (8) The inversion rate for $\alpha \rightarrow \beta$ is identical with the C1 acetoxy exchange rate for penta-*O*-acetyl-α-D-glucopyranose, whereas the C1 acetoxy exchange rate is about 17 times as rapid as the $\beta \rightarrow \alpha$ inversion rate for penta-*O*-acetyl-β-D-glucopyranose.[6]

Several mechanisms have been proposed to rationalize groups of these facts pertaining to the anomerization reaction. In 1951, we suggested[3] on the basis of polarimetric rate data that the known kinetic features of anomerization could be explained by the intervention of two reactions, 2 and 3, the essential anomerization step involving an SN2 attack by the conjugate acid of acetic anhydride on

$$Ac_2O + H_2SO_4 \rightleftharpoons Ac_2OH^{\oplus} + HSO_4^{\ominus} \quad (2)$$



(3)

(1) We are grateful to the Quaker Oats Co. for their generous support of a portion of this research.

(2) *Cf.* ref. 3 for a number of preparative examples.

(3) W. A. Bonner, THIS JOURNAL, **73**, 2659 (1951).
(4) E. B. Painter, *ibid.*, **75**, 1137 (1953).
(5) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **30**, 295 (1952).
(6) R. U. Lemieux, C. Brice and G. Huber, *ibid.*, **33**, 134 (1955).
(7) W. A. Bonner, THIS JOURNAL, **81**, 1448 (1959).
(8) W. A. Bonner, *ibid.*, **80**, 3372 (1958).
(9) W. A. Bonner, *ibid.*, **80**, 3697 (1958).