Experimental[13]

Mucochloric acid (technical grade) was obtained from the Quaker Oats Co. through the courtesy of Dr. A. P. Dunlop. Two recrystallizations from water (charcoal) gave white plates, m.p. 124–126°.

Sodium β-Formyl-β-keto-α-nitropropionate Dihydrate (III).—A solution of 65.7 g. (0.90 mole) of sodium nitrite in 80 ml. of water was stirred in a 1-l. r.b. flask while a solution of 50.7 g. (0.30 mole) of mucochloric acid in 250 ml. of 95% alcohol was added during the course of 30 minutes. The temperature was maintained at 35 ± 2° by intermittent application of an ice-bath. After stirring for an additional 1.5 hours at 35°, the reaction mixture was cooled to −5° in a salt–ice-bath and the pale yellow solid product was collected on a Buchner funnel and finally dried in a vacuum desiccator over anhydrous calcium chloride. The yield of crude product was 65.7 g. (96% yield). Two recrystallizations from dilute ethanol gave an analytical sample which had no melting point below 300° and exploded when heated on a spatula over an open flame.

Anal. Calcd. for $C_4H_6NO_8Na$: C, 21.93; H, 2.76; N, 6.39. Found: C, 21.63; H, 2.70; N, 6.37.

S-Benzylisothiouronium β-Formyl-β-keto-α-nitropropionate.—A solution of 1.01 g. of S-benzylisothiouronium chloride in 20 ml. of water was added to a solution of 0.91 g. of crude III in 20 ml. of water. The solution was filtered to remove a trace of brown solid and then stored in the refrigerator for 0.5 hour. Scratching the walls of the flask initiated the precipitation of a mass of fine, pale yellow crystals, which were collected and washed with two 5-ml. portions of water. Drying in air gave 0.92 g. of the salt (62% yield), in the form of fine, very light tan clusters. A reproducible decomposition point was obtained on this material by placing the capillary in the melting point bath at 70°, heating it up to 100° in three minutes, then to 110° in two more minutes and finally continuing to raise the temperature at the rate of 2°/minute. In this way a vigorous decomposition was obtained at 114°.

Anal. Calcd. for $C_{12}H_{13}O_6N_3S$: C, 44.03; H, 4.00; N, 12.84. Found: C, 43.73; H, 4.28; N, 13.10.

S-Benzylisothiouronium Nitromalonaldehyde.—A warm solution of 0.78 g. of sodium nitromalonaldehyde monohydrate in 10 ml. of water was mixed with a warm solution of 1.01 g. of S-benzylisothiouronium chloride in 10 ml. of water. Cooling in the refrigerator gave short, thick, light-tan prisms which were collected, washed with two 10-ml. portions of cold water and dried overnight in a vacuum pistol at room temperature, m.p. 120.5–121.5° dec.

Anal. Calcd. for $C_{11}H_{13}O_4N_3S$: C, 46.64; H, 4.62; N, 14.83. Found: C, 46.50; H, 4.66; N, 14.91.

Nitropyruvaldehyde Phenylosazone (IX).—To a solution of 1.44 g. of phenylhydrazine hydrochloride in a mixture of 20 ml. of water, 1.5 ml. of concentrated hydrochloric acid and 2 ml. of ethanol was added a solution of 0.66 g. of crude sodium β-formyl-β-keto-α-nitropropionate dihydrate (III) in 10 ml. of water. After 0.5 hour at room temperature a small amount of gummy material was removed by filtration and the solution was allowed to stand for 18 hours at room temperature. The flask then contained a mass of fine, tan, crystalline material. On drying in air this weighed 0.54 (60% yield). It was recrystallized from 20 ml. of 95% ethanol to give flat, tan needles of IX, m.p. 150–151° dec.

Anal. Calcd. for $C_{15}H_{15}O_2N_5$: C, 60.59; H, 5.09; N, 23.56. Found: C, 60.95; H, 5.18; N, 23.02.

2-Nitromethylquinoxaline (X).—A solution of 8.64 g. of crude sodium β-formyl-β-keto-α-nitropropionate dihydrate in 160 ml. of water was mixed with a solution of 4.8 g. of *o*-phenylenediamine in a mixture of 16 ml. of acetic acid and 64 ml. of water. The mixture was heated in a steam-chest at 65–75° for 1.5 hours and then cooled and filtered to give 3.4 g. (46% over-all yield from mucochloric acid) of crude, tan 2-nitromethylquinoxaline. A sample purified by vacuum sublimation formed bright yellow clusters which turned orange in the m.p. capillary at 100–110° and melted to a dark red liquid at 122–123°.

Anal. Calcd. for $C_9H_7O_2N_3$: C, 57.14; H, 3.73; N, 22.21; neut. equiv., 189. Found: C, 57.25; H, 3.65; N, 22.39; neut. equiv. by titration in 50% aq. alcohol with 0.1 *N* aq. sodium hydroxide, using a glass electrode, 192.

Quinoxaline-2-carboxylic Acid.—A mixture of 1.9 g. of crude 2-nitro-methylquinoxaline, 7 g. of potassium permanganate, 1 g. of sodium hydroxide and 200 ml. of water was heated on the steam-bath for one hour. The manganese dioxide was removed by filtration and the filtrate was acidified with concentrated hydrochloric acid to give a precipitate of quinoxaline-2-carboxylic acid, m.p. 210° (the literature value[14] is variously reported as 208–209, 210 and 212°).

(13) All melting points are corrected, unless otherwise stated. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

(14) Reference 10b, p. 251.

CHICAGO 16, ILL.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Aryl Amines. XXI. Effect of 3-Substituents on the Optical Stability of Some N-Benzenesulfonyl-N-carboxymethylmesidines

BY ROGER ADAMS AND J. S. DIX[1]

RECEIVED FEBRUARY 15, 1958

Expansion of the study of the optical activity of 3-substituted N-benzenesulfonyl-N-carboxymethylmesidines to include the 3-*t*-butyl and 3-methyl derivatives indicates that any inductive effect of an alkyl group apparently is minor. The low optical stability of the *t*-butyl compound may be an unexpected result of steric effects.

The influence of a 4-substituent on the optical stability of N-benzenesulfonyl-N-carboxymethyl-1-amino-2-methylnaphthalenes has been demonstrated by previous investigations of these compounds.[2–4]

To determine the extent to which field effects alone might influence the optical stability of such systems, a series of five compounds having various *m*-substituted benzyl groups attached to the 3-position of N-benzenesulfonyl-N-carboxymethylmesidine (I) has previously been studied.[5] Apparently there is little variation of optical stability with change in field. The minimum and maximum half-lives observed in the various substituted benzyl derivatives studied were 11.3 and 12.3 hr. and the two examples of extreme difference of electronic character of the groups gave essentially the same values; X = CN, half-life 12.1 hr.; and X = CH_3O, half-life 12.3 hr.

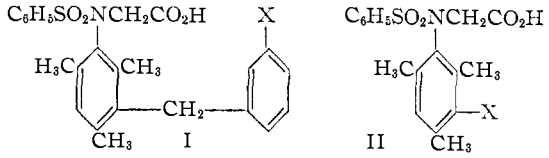
(1) University of Illinois Fellow, 1954–1955; Standard Oil of California Fellow, 1955–1957.

(2) R. Adams and R. H. Mattson, THIS JOURNAL, **76**, 4925 (1954).

(3) R. Adams and K. V. Y. Sundstrom, *ibid.*, **76**, 5474 (1954).

(4) R. Adams and H. H. Gibbs, *ibid.*, **79**, 170 (1957).

(5) R. Adams and K. R. Brower, *ibid.*, **78**, 663 (1956).



To determine possible inductive and steric influences on optical activity, a series of 3-substituted N-benzenesulfonyl-N-carboxymethylmesidines (II) was resolved and racemized.[6] The compounds, with the exception of the nitro derivative (half-life, 1.7 hr.), exhibited little variation (half-lives, 6.9–7.6 hr.)[6a] in optical stability. It is possible that because of the dipolar oxygen–nitrogen bond, the nitro group exerts an inductive influence. It has been shown that ethyl *m*-nitrobenzoate saponifies at a markedly faster rate than ethyl benzoate, whereas the effect of a *m*-amino substituent is much less.[7]

In none of the compounds is a steric effect evident. However, the series of 3-benzyl derivatives of N-benzenesulfonyl-N-carboxymethylmesidines is of considerably greater optical stability. This fact may indicate that a benzyl substituent crowds the *o*-methyl group, causing more hindrance to rotation about the ring carbon–nitrogen bond. Such a buttressing effect has previously been noted in the biphenyl series.[8]

It was the purpose of the present investigation to expand the study of mesidine derivatives to include a 3-substituent sterically more demanding than a benzyl group, which might thus be expected to exert a pronounced buttressing effect. The compound chosen was N-benzenesulfonyl-N-carboxymethyl-*t*-butylmesidine. To determine the possible inductive effect of an alkyl substituent, the 3-methyl analog also was prepared and studied.

The isoduridine derivative possesses a half-life (7.3 hr.) very similar to the corresponding benzyl derivatives. Any inductive effect of an alkyl group apparently is minor. The *t*-butyl compound, however, exhibits a pronounced decrease in optical stability (half-life, 1.5 hr.), a result that was not predicted. Whether the bulky *t*-butyl group has a different effect upon the ground state than on the transition state of the molecule relative to less bulky 3-substituents is difficult to say. A comparison of the half-lives of the corresponding 3-ethyl and 3-isopropyl derivatives with the methyl and *t*-butyl derivatives should serve to point up the relative steric effects.

The two mesidine derivatives were formed by nitration of the appropriate hydrocarbon, reduction of the nitro group, and introduction of the benzenesulfonyl and carboxymethyl groups onto the amino nitrogen. Synthesis of *t*-butylmesitylene was achieved by the reaction of *t*-butyl chloride and mesitylmagnesium bromide. That no rearrangement occurred in the nitration of *t*-butylmesitylene was shown when reduction of *t*-butylmesidine diazonium chloride yielded only *t*-butylmesitylene and chloro-*t*-butylmesitylene.

Acknowledgment.—The authors are indebted to Mrs. Maria Stingl, Miss Claire Higham and Mr. Josef Nemeth for performing the microanalyses and to Mr. James Brader for the determination and interpretation of infrared spectra.

Experimental

All melting points are corrected.

t-**Butylmesitylene.**—Mesitylmagnesium bromide was prepared by the gradual addition of 80.0 g. of bromomesitylene in 150 ml. of dry ether to 10.0 g. of magnesium turnings. To this reaction mixture was added 18.5 g. of *t*-butyl chloride, and heat applied for 0.5 hour until no magnesium remained. The heat was removed and 37.0 g. of *t*-butyl chloride was added over a period of 0.75 hour. Heat was applied and the solution kept at reflux temperature for 5 hours, then allowed to stand overnight.

The reaction mixture was decomposed with aqueous ammonium chloride and extracted with ether. After drying, the solvent was removed and the residual oil fractionally distilled to yield 31.7 g. of mesitylene, b.p. 50–52° (11 mm.), and 9.3 g. of crude *t*-butylmesitylene, b.p. 95–103° (11 mm.).

The latter fraction contained some bromomesitylene and was purified for elemental analysis by chromatography, using an activated alumina column and *n*-pentane as eluent. The hydrocarbon, which eluted before bromomesitylene, boiled at 108–109° (11 mm.), $n^{24}D$ 1.5006.

Anal. Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44. Found: C, 87.95; H, 11.77.

Preparation of Nitroalkylmesitylenes.—A solution of 0.3 mole of the 3-alkylmesitylene in 60 ml. of acetic anhydride was cooled to −20° and maintained at this temperature while a solution of 13.7 ml. of yellow fuming nitric acid (sp. gr. 1.5), 12 ml. of acetic anhydride and 12 ml. of glacial acetic acid was added with stirring over a period of 15 minutes. The reaction mixture was allowed to warm to room temperature, then poured into ice-water. The oil layer which separated was removed, and the aqueous portion extracted with ether. The oil and ether extracts were combined and washed repeatedly with water. The ethereal solution was dried, the solvent removed at atmospheric pressure, and the residual oil distilled at reduced pressure. Yields of 34% of crude nitroisodurene, b.p. 122–126° (10 mm.), and 37% of crude 3-nitro-*t*-butylmesitylene, b.p. 156–159° (10 mm.), were obtained. The crude nitro compounds were converted without purification to the corresponding amines.

Preparation of Alkylmesidines.—The nitro compounds were reduced by the method of Balcom and Furst,[9] employing hydrazine hydrate and Raney nickel catalyst. Crude isoduridine was obtained in 50% yield. It was identified by forming the N-acetyl derivative, m.p. 214–217° (lit.[10] m.p. 215°).

Crude *t*-butylmesidine was obtained in 71% yield as the hydrochloride. The pure base distilled at 162.5° (13 mm.), $n^{25}D$ 1.5502.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.61; H, 11.06. Found: C, 81.36; H, 10.95.

Diazotization and Reduction of *t*-**Butylmesidine.**—To a suspension of 4.23 g. of *t*-butylmesidine hydrochloride in 25 ml. of 6 *N* hydrochloric acid at −8° was added 1.6 g. of 97% sodium nitrite in 20 ml. of water, over a 45-minute period. Then 50 ml. of hypophosphorus acid was added, keeping the temperature at −8°. After standing at 5° for 36 hours, the mixture was extracted with ether. The ethereal extracts were washed with 15% aqueous sodium hydroxide, then water, and dried. After removal of solvent, distillation yielded 1.08 g. of a yellow oil, b.p. 96° (0.8 mm.), −96° (0.5 mm.). Elution with *n*-hexane on an alumina column gave 0.60 g. of a colorless oil. Distillation of this material in a Kugelrohr at 140° (15 mm.) yielded 0.15 g. of *t*-butylmesitylene, identified by its infrared spectrum and elemental analysis. A second compound weighing 0.38

(6) R. Adams and M. J. Gortatowski, THIS JOURNAL, **79**, 5525 (1957).

(6a) These values are somewhat higher than those reported in ref. 6, which were calculated by a slightly different method. By recalculation of the half-lives from the same experimental data in the manner used in previously published papers and in this paper, the revised values for the half-lives in hours are as follows: NO_2, 1.7; Cl, 6.9; Br, 7.6; I, 7.2; NH_2, 7.0.

(7) K. Kindler, *Ann.*, **450**, 1 (1926).

(8) H. C. Yuan and R. Adams, THIS JOURNAL, **54**, 4434 (1932).

(9) D. Balcom and A. Furst, *ibid.*, **75**, 4334 (1953).

(10) L. I. Smith and J. H. Paden, *ibid.*, **56**, 2169 (1934).

g. also was isolated. Elemental analysis indicated it to be chloro-*t*-butylmesitylene.

Anal. Calcd. for $C_{13}H_{19}Cl$: C, 74.09; H, 9.09. Found: C, 73.98; H, 8.90.

Preparation of N-Benzenesulfonylalkylmesidines.—To a pyridine solution of the crude amine hydrochloride was added 1.2 molar equivalents of benzenesulfonyl chloride. The solution was heated at 60–70° for one hour, cooled, and poured into a mixture of ice and hydrochloric acid. The material which precipitated was recrystallized from 95% ethanol until a constant melting point was attained. A yield of 62% of N-benzenesulfonylisoduridine, m.p. 178–179°, was obtained.

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84. Found: C, 66.44; H, 6.74; N, 5.13.

N-Benzenesulfonyl-*t*-butylmesidine, m.p. 177–178°, was formed in 48% yield.

Anal. Calcd. for $C_{19}H_{25}NO_2S$: C, 68.84; H, 7.60; N, 4.23. Found: C, 68.65; H, 7.85; N, 4.50.

Preparation of N-Benzenesulfonyl-N-carboxymethylalkylmesidines.—To a warm, stirred ethanolic solution of the N-benzenesulfonylalkylmesidine and 2 molar equivalents of potassium ethoxide was added 1.2 molar equivalents of ethyl bromoacetate. Precipitation of potassium bromide occurred immediately. After heating for 40 minutes, the mixture was cooled and the precipitate collected. The solid was washed with hot ethanol, and the wash combined with the original filtrate. To this solution was added a large excess of 20% aqueous sodium hydroxide and the solution was heated until all the ethanol had distilled. Water was added periodically to maintain a nearly constant volume. The residual solution was heated an additional 3 hours, cooled, and made acid to congo red with cold concd. hydrochloric acid. The solid which precipitated was dissolved in aqueous sodium carbonate, the solution filtered, and the acid reprecipitated. Recrystallization was achieved from benzene. A yield of 71% of N-benzenesulfonyl-N-carboxymethylisoduridine was obtained.

Anal. Calcd. for $C_{18}H_{21}NO_4S$: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.42; H, 5.81; N, 4.13.

N-Benzenesulfonyl-N-carboxymethyl-*t*-butylmesidine also formed in 71% yield.

Anal. Calcd. for $C_{21}H_{27}NO_4S$: C, 64.76; H, 6.98; N, 3.60. Found: C, 64.62; H, 7.11; N, 3.83.

Resolution of N-Benzenesulfonyl-N-carboxymethylisoduridine.—A solution of 4.20 g. of N-benzenesulfonyl-N-carboxymethylisoduridine, 3.54 g. of cinchonine and 325 ml. of ethyl acetate was prepared by warming the mixture and filtering the hot solution. The volume was reduced to 200 ml. by passing an air stream over the solution at room temperature. The solution was cooled in a refrigerator for several days, and 2.85 g. of colorless prisms was collected, m.p. 185–188°. After recrystallization from ethyl acetate the melting point was 186–188°, and the specific rotation unchanged; rotation: 0.0508 g. made up to 10 ml. at 30° with ethanol gave α_D +0.50°, *l* 1; $[\alpha]^{30}_D$ +98.5°.

The optically active acid was regenerated from the pure salt in a manner previously described.[11] From 1.48 g. of the pulverized salt was obtained 0.75 g. (94%) of (+)-N-benzenesulfonyl-N-carboxymethylisoduridine, m.p. 184–186°; rotation: 0.0185 g. made up to 1.607 ml. with ethanol at 29° gave α_D +0.08°, *l* 1; $[\alpha]^{29}_D$ + 6.9°.

Racemization of N-Benzenesulfonyl-N-carboxymethylisoduridine.—A dimethylformamide solution of 0.7670 g. of the (+)-acid was made up to 10 ml. and the racemization carried out at 118° (boiling point of *n*-butyl alcohol) in a manner described previously.[3] The following results were obtained: 0.0 hr., α^{30}_D +0.22°; 1.5 hr., α^{30}_D +0.19°; 2.5 hr., α^{30}_D +0.17°; 4.0 hr., α^{30}_D +0.15°; 5.0 hr., α^{30}_D +0.14°; 6.0 hr., α^{30}_D +0.13°.

The expression for the racemization rate of compounds exhibiting optical activity of the type studied is: $\ln \alpha_0/\alpha_t = 2kt$, where α_0 is the observed rotation at time 0 and α_t is the observed rotation at time *t*.[12] A plot of α *vs.* time on semi-logarithmic paper afforded a straight line from whose slope was derived the rate constant $k = 4.7 \times 10^{-2}$ hr.$^{-1}$ and the half-life $t_{1/2}$ = 7.3 hr.

Resolution of N-Benzenesulfonyl-N-carboxymethyl-*t*-butylmesidine.—The cinchonidine salt of N-benzenesulfonyl-N-carboxymethyl-*t*-butylmesidine was prepared in a manner similar to that of the cinchonine salt of the isoduridine derivative, using ethyl acetate as resolving solvent. The less soluble salt was purified by recrystallization from ethyl acetate, m.p. 195–196°; rotation: 0.0611 g. made up to 10 ml. at 28° with ethanol gave α_D −0.22°, *l* 1; $[\alpha]^{28}_D$ −36.0°. It was treated in the manner previously described to yield pure (+)-N-benzenesulfonyl-N-carboxymethyl-*t*-butylmesidine, m.p. 171.5–172.5°; rotation: 0.0064 g. made up to 1.607 ml. with ethanol at 26° gave α_D +0.17°, *l* 1; $[\alpha]^{25}_D$ +42.5°.

Racemization of N-Benzenesulfonyl-N-carboxymethyl-*t*-butylmesidine.—A dimethylformamide solution of 0.1542 g. was made up to 10 ml. and the racemization carried out in the usual manner. The following results were obtained: 0.0 hr., α^{26}_D +0.58°; 0.75 hr., α^{26}_D +0.42°; 1.5 hr., α^{26}_D +0.30°; 2.0 hr., α^{26}_D +0.24°; 3.0 hr., α^{26}_D +0.14°; 4.0 hr., α^{26}_D +0.09°. The rate constant derived was $k = 2.32 \times 10^{-1}$ hr.$^{-1}$ and the half-life, $t_{1/2}$ = 1.49 hr.

(11) R. Adams and J. R. Gordon, THIS JOURNAL, **72**, 2456 (1950).

(12) D. F. Smith, *ibid.*, **49**, 43 (1927).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Reaction of Hydroxylamine with Activated Acyl Groups. I. Formation of O-Acylhydroxylamine[1]

BY WILLIAM P. JENCKS[2]

RECEIVED FEBRUARY 3, 1958

The reaction of *p*-nitrophenyl acetate or benzoate with dilute aqueous or alcoholic hydroxylamine at neutral *p*H gives as a major initial product an unstable compound which has been identified as the corresponding O-acylhydroxylamine. These compounds give no color with ferric chloride, are rapidly split by dilute base and react with concentrated hydroxylamine to give hydroxamic acid. Evidence for the formation of varying amounts of O-acylhydroxylamines with other acylating agents has been obtained.

Although the reactions of hydroxylamine with chlorosulfonic acid[3] and (on the basis of indirect evidence) certain phosphoric anhydrides[4] give O-substituted compounds, the products isolated from the reaction of hydroxylamine with acylating agents have been N-substituted hydroxylamines (hydroxamic acids)[5] with the apparent single exception of O-anthranoylhydroxylamine, which is formed from hydroxylamine and isatoic anhydride.[6] This re-

(1) For a preliminary report see W. P. Jencks, *Biochim. et Biophys. Acta*, **27**, 417 (1958).

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(3) F. Sommer, O. F. Schulz and M. Nassau, *Z. anorg. allgem. Chem.*, **147**, 142 (1925).

(4) B. Jandorf, THIS JOURNAL, **78**, 3686 (1956).

(5) H. L. Yale, *Chem. Revs.*, **33**, 209 (1943); F. Mathis, *Bull. soc. chim.*, **20**, D 9 (1953).

(6) A. W. Scott and B. L. Wood, *J. Org. Chem.*, **7**, 508 (1942).