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

# Restricted Rotation in Aryl Amines. XII. Resolution of Certain N-Benzenesulfonyl-N-carboxymethyl Derivatives

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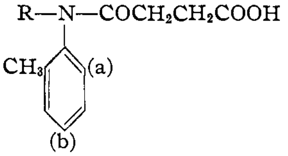
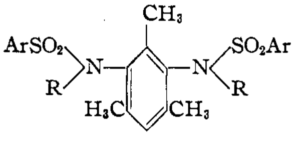
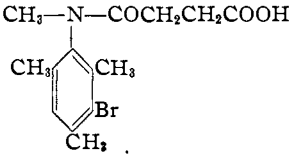
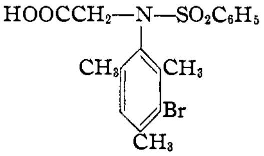
A variety of aromatic amines of the general structure I, in which various combinations of groups were present, where R was methyl or ethyl, where (a) was methyl, bromine, nitro, iodine, methoxyl and where (b) was methyl, chlorine or bromine, have been prepared and resolved.[2] Many molecules of type II in which two points of restricted rotation are present have been isolated in *cis* and *trans* forms. When R was —$CH_2COOH$, the *trans* form was resolved.[3]


I

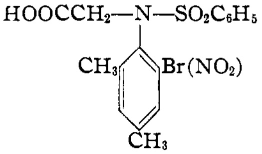

II

A comparison has now been made of the stability of compounds III and IV in order to determine in the same amine the relative effect of different substituents on the nitrogen atom, the N-methyl-N-succinyl as compared with the N-benzenesulfonyl-N-carboxymethyl groupings. Compound III has been previously described and the half-life of the active form is nine hours in boiling butanol.[2a] Compound IV has a half-life under similar conditions of eight hours. This decrease in stability in IV might be explained on the basis of the decrease in basicity of IV due to the more acid nature of the combination of benzenesulfonyl and the carboxymethyl groups on the nitrogen atom.


III


IV

Yuan[4] has reported that he was unsuccessful in resolving compounds V and VI. The successful resolution described in an earlier paper[2d] of compounds which differ from those of Yuan only by the substitution of the N-methyl-N-succinyl for the N-benzenesulfonyl-N-carboxymethyl groupings and the slight difference in stability observed in compounds III and IV made it appear anomalous that compounds V and VI could not be resolved. For this reason compounds V and VI were subjected to reinvestigation.


Br = V, $NO_2$ = VI

Successful resolution is often critically dependent upon minor factors such as the selection of the appropriate solvent or active resolving agent employed. A study of alkaloids for resolution other than those investigated by Yuan was, therefore, made. It was found that the bromo compound (V) formed a well-crystallized cinchonidine salt which was readily separated into two diastereoisomers. Hydrolysis gave the active form $[\alpha]^{28}\text{D} - 15°$, which racemized in boiling butanol with a half-life of two and one half hours. As expected, the observed value is slightly less than that for the corresponding N-succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene (three and one-tenth hours). The nitro compound (VI) was converted to the cinchonine salt as described by Yuan. Although only a single salt resulted, this salt mutarotated indicating that resolution could be effected. The half-life of the salt was thirty-two hours in absolute ethanol at 31°. By decomposition of the salt at low temperature, the optically active nitro compound resulted which had a half-life in boiling methyl acetate of 2.25 hr.; at 29° in the same solvent, the half-life was sixty-five hours. According to previously suggested factors influencing the stability of the optically active forms of molecules of this type, this compound should be less rather than more stable than N-succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene (half-life 0.6 hr. in boiling methyl acetate). A discussion of the anomaly will be included in a future communication describing a comparison of other nitro compounds of a similar type.

Compound IV was synthesized by benzenesulfonation of bromoaminomesitylene followed by introduction of the carboxymethyl group by means of methyl bromoacetate in presence of sodium methoxide and then saponification. It was resolved through the cinchonidine salt.

Compound V was prepared as described by

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[1] An abstract of a thesis submitted by Joseph R. Gordon to the Graduate College of the University of Illinois, 1949, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] (a) Adams and Dankert, THIS JOURNAL, **62**, 2191 (1940); (b) Adams and Stewart, *ibid.*, **63**, 2859 (1941); (c) Adams and Albert, *ibid.*, **64**, 1475 (1942); (d) Adams and Sundholm, *ibid.*, **70**, 2667 (1948); (e) Adams and Gordon, *ibid.*, **72**, 2454 (1950).

[3] Adams and Tjepkema, *ibid.*, **70**, 4204 (1948); Adams and Rothstein, *ibid.*, **71**, 1620 (1949); Adams and Campbell, *ibid.*, **72**, 128 (1950); Adams and Nelson, *ibid.*, **72**, 132 (1950); Adams and Englund, *ibid.*, **72**, 135 (1950).

[4] Yuan, *J. Chinese Chem. Soc.*, **4**, 131 (1936).

Yuan,[4] with the exception that the carboxymethyl group was introduced by means of methyl bromoacetate in the presence of sodium methoxide in methanol, followed by saponification. Compound VI was synthesized according to the previously described procedure[4] except that the nitration of N-benzenesulfonyl-1-amino-2,4-dimethylbenzene was found to proceed more readily at room temperature than at 70°.

## Experimental

**N-Benzenesulfonyl-3-bromomesidine.**—To a solution of 12.6 g. of 3-bromomesidine[2a] in 40 ml. of pyridine was added with stirring a solution of 10.6 g. of benzenesulfonyl chloride in 35 ml. of pyridine. The mixture was cooled and then poured into 200 ml. of ice water. The product was collected and recrystallized from ethanol. It formed white crystals, m. p. 181.5–182° (cor.). The yield was 17 g. (77%).

*Anal.* Calcd. for $C_{16}H_{16}NO_2SBr$: C, 50.84; H, 4.53. Found: C, 50.95; H, 4.64.

**N-Benzenesulfonyl-N-carbomethoxymethyl-3-bromomesidine.**—To a solution of 3.68 g. of sodium methoxide in 60 ml. of methanol was added 10.4 g. of methyl bromoacetate and 12.6 g. of 3-bromomesidine. The solution was refluxed for twenty hours and then poured into 500 ml. of hot water. The oil that separated solidified and was recrystallized from acetic acid. It formed white crystals, m. p. 95.0–95.5° (cor.). The yield was 10.0 g. (67%).

*Anal.* Calcd. for $C_{18}H_{20}NO_4SBr$: C, 50.71; H, 4.73. Found: C, 50.91; H, 4.68.

**N-Benzenesulfonyl-N-carboxymethyl-3-bromomesidine.**—To a solution of 100 ml. of glacial acetic acid and 75 ml. of 1:10 sulfuric acid was added 9.5 g. of N-benzenesulfonyl-N-carbomethoxymethyl-3-bromomesidine. The mixture was refluxed two hours, cooled and poured into 1 l. of water. The product was collected and recrystallized from 80% acetic acid. It formed white crystals, m. p. 211–212° (cor.). The yield was 8.9 g. (98%).

*Anal.* Calcd. for $C_{17}H_{18}NO_4SBr$: C, 49.53; H, 4.41. Found: C, 49.94; H, 4.81.

**Resolution of N-Benzenesulfonyl-N-carboxymethyl-3-bromomesidine.**—A solution of 5.0 g. of N-benzenesulfonyl-N-carboxymethyl-3-bromomesidine and 3.58 g. of cinchonidine in 80 ml. of ethyl acetate was filtered and then placed in a refrigerator overnight. Crystals weighing 2.00 g. were collected. Succeeding fractions were obtained as shown in the following table. The specific rotation readings were taken by making 0.06 g. of the salt up to 20 ml. with absolute ethanol. A one-decimeter tube was used.

| Crop | g. | $\alpha_D$ at 23° | $[\alpha]^{23}_D$ | Vol. in ml. |
|---|---|---|---|---|
| I | 2.00 | −0.146° | −49° | 80 |
| II | 1.31 | − .137 | −46 | 70 |
| III | 1.99 | − .159 | −53 | 25 |
| IV | 0.76 | − .165 | −55 | 15 |
| V | 0.77 | − .171 | −57 | 5 |
| VI | 0.21 | | | 0 |

Crops I and II containing 39% of the total amount present were recrystallized from 50 ml. of ethyl acetate. The following results were obtained.

| Crop | Wt., g. | $\alpha_D$ at 23° | $[\alpha]^{23}_D$ | Vol. in ml. |
|---|---|---|---|---|
| A | 1.92 | −0.147° | −49° | 50 |
| B | 0.23 | − .156 | −50 | 40 |
| C | .19 | − .148 | −49 | 20 |
| D | .18 | | | 0 |

Crops A, B and C, having identical rotations, were accepted as the pure less-soluble salt (*l*B*l*A). It formed white feathery crystals, m. p. 136–137° (cor.).

*Rotation.* 0.06 g. made up to 20 ml. with absolute ethanol at 23° gave $\alpha_D$ −0.147°; *l*, 1; $[\alpha]^{23}_D$ −49°.

*Anal.* Calcd. for $C_{17}H_{18}NO_4SBr \cdot C_{19}H_{22}N_2O$: C, 61.19; H, 5.71. Found: C, 60.27; H, 6.17.

***d*- and *l*-N-Benzenesulfonyl-N-carboxymethyl-3-bromomesidine.**—The pure less-soluble salt (2.28 g.) was decomposed with cold 1:1 hydrochloric acid in the manner previously described. The product formed white crystals, m. p. 212–214° (cor.). The yield was 0.94 g.

*Rotation.* 0.203 g. made up to 20 ml. with absolute ethanol at 25° gave $\alpha_D$ −0.117°; *l*, 2; $[\alpha]^{25}_D$ −6°.

*Anal.* Calcd. for $C_{17}H_{18}NO_4SBr$: C, 49.53; H, 4.41. Found: C, 49.63; H, 4.22.

The more-soluble salt, crops IV and V, 1.34 g., was decomposed with cold 1:1 hydrochloric acid in the usual manner. The product melted at 211–214°. The yield was 0.54 g.

*Rotation.* 0.198 g. made up to 20 ml. with absolute ethanol at 27° gave $\alpha_D$ +0.111°; *l*, 2; $[\alpha]^{27}_D$ +6°.

**Racemization of N-Benzenesulfonyl-N-carboxymethyl-3-bromomesidine.**—A solution of 0.29 g. of the *l*-acid in 20 ml. of butanol was racemized in the manner previously described.[2c] The average rate constant was $4.59 \times 10^{-2}$ hr.$^{-1}$; half-life period, 7.7 hr. ± 1.5 hr. A check racemization in butanol resulted in an average rate constant of $4.21 \times 10^{-2}$ hr.$^{-1}$; half-life period, 8.2 hr. ± 1.0 hr.

**N-Benzenesulfonyl-N-carbomethoxymethyl-1-amino-2,4-dimethyl-6-bromobenzene.**—To a solution of 2.0 g. of sodium methoxide in 60 ml. of methanol was added 11.3 g. of N-benzenesulfonyl-1-amino-2,4-dimethyl-6-bromobenzene and 11.0 g. of methyl bromoacetate. The mixture was refluxed for twenty hours and then poured into 500 ml. of hot water. An oil separated which could not be crystallized.

**N-Benzenesulfonyl-N-carboxymethyl-2,4-dimethyl-6-bromobenzene.**—The oil which was assumed to be N-benzenesulfonyl-N-carbomethoxymethyl-1-amino-2,4-dimethyl-6-bromobenzene was added to a solution of 50 ml. of glacial acetic acid, 5 ml. of concentrated sulfuric acid and 20 ml. of water. The mixture was refluxed for eight hours and cooled. Then 200 ml. of water was added and the aqueous ammonia until neutralized. The mixture was filtered and the filtrate acidified with hydrochloric acid. An oil separated which crystallized on standing. The product was recrystallized from ethanol as white crystals, m. p. 196–197° (cor.). The yield was 10.4 g. (78%). Yuan[4] reports m. p. 196–197°.

**Resolution of N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-bromobenzene.**—A solution of 4.28 g. of N-benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-bromobenzene and 3.08 g. of cinchonidine in 85 ml. of a mixture of 9:1 ethyl acetate and methanol by volume was filtered and placed in a refrigerator overnight. Crystals weighing 2.28 g. were collected. Succeeding fractions were obtained as shown in the following table. The specific rotation readings were taken by making 0.06 g. of the salt up to 20 ml. with absolute ethanol. A one-decimeter tube was used.

| Crop | Wt., g. | $\alpha_D$ at 24° | $[\alpha]^{24}_D$ | Vol. in ml. |
|---|---|---|---|---|
| I | 2.28 | −0.225° | −75.1° | 85 |
| II | 0.86 | − .220 | −73.2 | 50 |
| III | 0.74 | − .224 | −74.8 | 30 |
| IV | 2.40 | − .228 | −76.0 | 0 |

Crops I and II containing 43% of the total amount present were recrystallized from a 9:1 ethyl acetate and methanol solution. From this solution 2.05 g. of salt was collected. This fraction was the pure less-soluble salt (*l*B*l*A). It formed white feathery crystals, m. p. 180–180.5° (cor.).

*Rotation.* 0.06 g. made up to 20 ml. with absolute ethanol at 24° gave $\alpha_D$ −0.208°; *l*, 1; $[\alpha]^{24}_D$ −69.3°.

*Anal.* Calcd. for $C_{16}H_{16}NO_4BrS \cdot C_{14}H_{22}N_2O$: C, 60.69; H, 5.53. Found: C, 60.50; H, 5.70.

***d*- and *l*-N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-bromobenzene.**—The pure less-soluble salt (1.90 g.) was decomposed with cold 1:1 hydrochloric acid in the manner previously described. It formed white crystals, m. p. 196–198° (cor.). The yield was 1.20 g.

*Rotation.* 0.196 g. made up to 20 ml. with absolute ethanol at 28° gave $\alpha_D$ $-0.296°$; $l$, 2; $[\alpha]^{28}_D$ $-15°$.

*Anal.* Calcd. for $C_{16}H_{16}NO_4SBr$: C, 48.13; H, 4.04. Found: C, 48.01; H, 4.32.

The more-soluble salt (crop IV, 2.30 g.) was decomposed with cold 1:1 hydrochloric acid in the usual manner, m. p. 196–198° (cor.). The yield was 1.02 g.

*Rotation.* 0.2035 g. made up to 20 ml. with absolute ethanol at 28° gave $\alpha_D$ $+0.297°$; $l$, 2; $[\alpha]^{28}_D$ $+15°$.

**Racemization of N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-bromobenzene.**—With *n*-butanol as a solvent, 0.23 g. of the *l*-acid in 20 ml. was racemized in the usual way. The average rate constant was $1.30 \times 10^{-1}$ hr.$^{-1}$; half-life period, 2.7 hr. ± 0.75 hr. A check racemization in *n*-butanol gave an average rate constant of $1.44 \times 10^{-1}$ hr.$^{-1}$; half-life period, 2.4 hr. ± 0.2 hr.

**N-Benzenesulfonyl-1-amino-2,4-dimethyl-6-nitrobenzene.**—Urea was added to 100 ml. of fuming nitric acid (sp. gr. 1.49) until the acid became colorless. It was then cooled to 20° and 26 g. of N-benzenesulfonyl-1-amino-2,4-dimethylbenzene was added with stirring. The temperature was kept between 20–30° by means of an ice-bath. The solution was allowed to stand at room temperature for four hours and then poured into 1 l. of water. The product was collected and recrystallized from ethanol. It formed white crystals, m. p. 154–156°. The yield was 19 g. (62%). Rabout[5] reports a m. p. of 153°. Yuan[4] reports a m. p. of 156°.

**N-Benzenesulfonyl-N-carboethoxymethyl-1-amino-2,-4-dimethyl-6-nitrobenzene.**—To a solution of 1.38 g. of sodium in 60 ml. of absolute ethanol was added 9.16 g. of N-benzenesulfonyl-1-amino-2,4-dimethyl-6-nitrobenzene and 10.0 g. of ethyl bromoacetate. The mixture was refluxed twelve hours and then poured into 1 l. of water. The mixture was acidified with acetic acid and cooled in ice. The oil which separated crystallized on standing. The product which was recrystallized from ethanol formed white crystals, m. p. 93–95°. The yield was 9.5 g. (81%). This is the same melting point reported by Yuan.[4]

**N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene.**[4]—A solution of 50 ml. of glacial acetic acid, 20 ml. of water, 2 ml. of concentrated sulfuric and 7.0 g. of N-benzenesulfonyl-N-carboethoxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene was refluxed for eight hours. The mixture was poured into 600 ml. of water and the crystalline product collected and recrystallized from ethanol as white crystals, m. p. 212–213°. The yield was 5.0 g. (77%). Yuan reports a m. p. 212°.

**Resolution of N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene.**—A solution of 2.34 g. of N-benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene in 50 ml. of ethyl acetate was added to a solution of 1.87 g. of cinchonine in 125 ml. of boiling ethanol. The mixture was evaporated to 65 ml. with the aid of a suction pump and then placed in a refrigerator overnight. From this solution 1.04 g. of crystals was collected. Solvent was removed from the mother liquor until the volume was 50 ml. and another 0.98 g. of crystals was collected. Solvent was again evaporated until the mother liquor was 15 ml., when 30 ml. of ethyl acetate was added. A third fraction of 0.25 g. of crystals was collected. The specific rotation readings were taken by making 0.05 g. up to 50 ml. with absolute ethanol. A two-decimeter tube was used.

| Crop | Wt., g. | $\alpha_D$ at 30° | $[\alpha]^{30}_D$ |
|---|---|---|---|
| I | 1.04 | 0.259° | 130 |
| II | 0.98 | .265 | 132 |
| III | 0.25 | .268 | 134 |

Several small fractions, averaging about 0.2 g. each, were then separated from the mother liquor. Their specific rotations were similar to the above fractions. Crystals were collected even at dryness.

A sample of crop I was recrystallized from ethyl acetate and an almost quantitative yield obtained. No oil was found when the residue was evaporated to dryness. No change in specific rotation of the recrystallized salt was noted. Only the *d*B*d*A salt could be isolated. The product formed white crystals, m. p. 193–195° (cor.).

*Rotation.* 0.05 g. made up to 50 ml. with absolute ethanol at 30° gave $\alpha_D$ $+0.259°$; $l$, 2; $[\alpha]^{30}_D$ $+130°$.

*Anal.* Calcd. for $C_{16}H_{16}N_2O_6S \cdot C_{19}H_{22}N_2O$: C, 63.95; H, 5.83. Found: C, 63.23; H, 5.74.

**Mutarotation of Cinchonine Salt of N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene.**—A sample of 0.10 g. of crop I was dissolved in 20 ml. of absolute ethanol. The solution was transferred to a two-decimeter tube. Rotations were taken at appropriate intervals. The temperature was 31°. The average rate constant was $1.03 \times 10^{-2}$ hr.$^{-1}$, half-life period 33 hr. ± 3 hr. A check mutarotation with 0.10 g. of the salt at 31° resulted in a rate constant of $1.11 \times 10^{-2}$ hr.$^{-1}$; half-life period 31 ± 5 hr.

***d*-N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene.**—The *d*B*d*A salt weighing 1.63 g. from the first three crops was decomposed with 1:1 hydrochloric acid cooled below 0° as previously described. The product formed white crystals, m. p. 214–215° (cor.). The yield was 0.85 g.

*Rotation.* 0.1063 g. made up to 20 ml. with absolute ethanol at 30° gave $\alpha_D$ $+2.519°$; $l$, 2; $[\alpha]^{30}_D$ $+236°$.

*Anal.* Calcd. for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.42. Found: C, 53.02; H, 4.72.

**Racemization of N-Benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene.**—A solution of 0.33 g. of the *l*-acid in 20 ml. of methyl acetate was poured into a two-decimeter tube. With the temperature at 29°, rotation readings were taken at intervals. The average rate constant was $5.36 \times 10^{-3}$ hr.$^{-1}$; half-life period 65 ± 2 hr.

A solution of 0.11 g. of the *d*-acid in 20 ml. of methyl acetate was racemized in the usual manner in the boiling solvent. The average rate constant was $1.53 \times 10^{-1}$ hr.$^{-1}$; half-life period 2.26 ± 0.06 hr. A check racemization resulted in an average rate constant of $1.54 \times 10^{-1}$ hr.$^{-1}$; half-life period 2.25 ± 0.10 hr.

## Summary

1. N-Benzenesulfonyl-1-carboxymethyl-3-bromomesidine, N-benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-bromobenzene and N-benzenesulfonyl-N-carboxymethyl-1-amino-2,4-dimethyl-6-nitrobenzene have been prepared and resolved into their active forms. The half-lives of racemization were determined.

2. The bromomesidine derivative had a half-life of eight hours in boiling *n*-butanol, while the bromoxylidine derivative had a half-life of two and one-half hours in the same solvent. The nitro compound had a half-life of two and one-quarter hours in boiling methyl acetate.

3. The decreased optical stability of these compounds over their N-succinyl-N-methyl analogs has been explained by the decreased basicity of the compounds caused by the acidic nature of the benzenesulfonyl and carboxymethyl groups on the nitrogen atom.

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(5) Rabout, *Bull. soc. chim. France*, [3] **15**, 1035 (1897).