

mate mixture (1:1) of this ester and authentic *p*-vinylphenyl benzoate, m.p. 75.5–76°, melted at 74.5–75.5°. The tosylate derivative, prepared under the same conditions, was recrystallized from aqueous ethanol to afford fine white needles, m.p. 66–67°. An intimate mixture (1:1) of this ester and authentic *p*-vinylphenyl tosylate,²² m.p. 68–68.5°, melted at 67–68°.

The allyloxy ether of *p*-vinylphenol was prepared for another study. *p*-Vinylphenyl benzoate (20.0 g., 0.0894 mole) was saponified as described earlier and a mixture of the crude product, 12.1 g. (0.100 mole) of allyl bromide, 15 g. of anhydrous potassium carbonate and 25 ml. of absolute ethanol was heated at the reflux temperature for 4 hours. At the completion of the reaction, 100 ml. of water and 100 ml. of petroleum ether (b.p. 60–68°) were added. The layers were separated and the organic layer was extracted with 5% sodium hydroxide solution and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was distilled under diminished pressure to give 4.59 g. (32% over-all) of colorless oil, b.p. 77–84° (1 mm.), n_D^{20} 1.5588. A center cut, b.p. 82–83°, n_D^{20} 1.5588, was selected for the analytical sample.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.21; H, 7.87.

The tetrabromide derivative was recrystallized from petroleum ether (b.p. 60–68°) to give thick white needles, m.p. 119.5–120°.

Anal. Calcd. for $C_{11}H_{12}OBr_4$: C, 27.53; H, 2.52. Found: C, 27.80; H, 2.73.

p-Vinylphenol from *p*-Vinylphenyl Tosylate.—A mixture of 7.50 g. (0.0274 mole) of *p*-vinylphenyl tosylate,²² 7.7 g. of potassium hydroxide dissolved in 40 ml. of water and 20 ml. of ethanol was stirred at room temperature for 4 days before complete solution was attained. The product was isolated in the same manner as described for the saponification of *p*-vinylphenyl benzoate to give 0.89 g. (27%) of product, m.p. 69–71°.

Reaction of *o*-Vinylphenol and *p*-Nitrobenzenediazonium Chloride.—*p*-Nitrobenzenediazonium chloride was prepared in the usual manner from 2.30 g. (0.0167 mole) of *p*-nitroaniline dissolved in a solution of 20 ml. of 5% hydrochloric acid and 50 ml. of water and 1.16 g. (0.0167 mole) of sodium nitrite dissolved in 20 ml. of water. The diazonium chloride solution was added dropwise, with stirring, to a cold (5°) solution of 2.00 g. (0.0167 mole) of *o*-vinylphenol, 2.8 g. of sodium hydroxide and 200 ml. of water. The reaction mixture was carbonated with Dry Ice after which a brick-

red solid separated. The solid was extracted with three 100-ml. portions of hot ethanol. The extracts were diluted with water and cooled and the solids which separated were collected and air-dried. The first extract gave 1.57 g. (35%) of crude mono-coupled product, m.p. 107–111° (softening at 78°). A sample recrystallized further from aqueous ethanol gave bright orange plates, m.p. 127–129° (softening at 123°).

Anal. Calcd. for $C_{14}H_{11}O_3N_3$: C, 62.46; H, 4.12. Found: C, 62.76; H, 4.52.

The benzoate ester, prepared under Schotten-Baumann conditions, was recrystallized from ethyl acetate-ethanol mixtures to give red needles, m.p. 153–155°.

Anal. Calcd. for $C_{21}H_{15}O_4N_3$: C, 67.55; H, 4.05. Found: C, 67.26; H, 4.14.

The solids which separated from the second and third extracts were combined to give 0.72 g. (10%) of crude di-coupled product, m.p. 174–186° dec. A sample recrystallized 5 times from ethyl acetate-ethanol mixtures gave an orange powder, m.p. 180–181° dec. The recrystallizations were not successful in removing all of the mono-coupled product.

Anal. Calcd. for $C_{20}H_{24}O_6N_6$: C, 57.41; H, 3.37. Found: C, 58.58; H, 3.90.

Reaction of *m*-Vinylphenol and *p*-Nitrobenzenediazonium Chloride.—*p*-Nitrobenzenediazonium chloride (0.0417 mole) was prepared as described in the previous experiment and added dropwise, with stirring, to a cold (5°) solution containing 5.00 g. (0.0417 mole) of *m*-vinylphenol, 7 g. of sodium hydroxide and 500 ml. of water. The solution, which had turned deep red during the addition, was carbonated with Dry Ice, after which a black tar separated. The tar was dissolved in hot ethanol and after a process of cooling, decanting the solution from tars which had separated, reheating and diluting the solution with water and cooling again, was repeated several times, there was obtained about 50 mg. of red needles, m.p. 163–165°. The product was dissolved in benzene and chromatographed through acid-washed alumina. The major band was retained. The solvent was removed by evaporation and the residue was recrystallized from aqueous ethanol to give fine red needles, m.p. 166–167°.

Anal. Calcd. for $C_{14}H_{13}O_3N_3$: C, 62.45; H, 4.12. Found: C, 62.81; H, 4.21.

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

Restricted Rotation in Aryl Amines. XXII. N-Benzenesulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine and its N-Oxide

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The synthesis of N-benzenesulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine (II) and its 1-oxide (III) is described. Unlike the analogous 3-substituted mesidines, which were readily resolvable, resolution of these pyridine compounds failed.

Free rotation of the substituted nitrogen atom about the pivot bond in N-benzenesulfonyl-N-carboxymethylmesidine (I) is inhibited by the two *o*-methyl groups, and asymmetry is imparted to the molecule by the presence of the *m*-substituent. Such compounds have been resolved into their respective enantiomorphs, and their rates of racemization have been measured.^{2,3} The present work

was undertaken to determine if N-benzenesulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine (II) might also exist as a *dl*-pair, since models indicate that free rotation of the substituted nitrogen atom about the pivot bond as in the benzene analogs (I) is inhibited by the two *o*-methyl groups. Asymmetry is introduced by the presence of the heterocyclic nitrogen atom in the *m*-position.

Compound II is such a weak acid that the salts with alkaloids were unstable. Various alkaloids and solvents were employed unsuccessfully in an effort to obtain an alkaloid salt of II suitable for resolution. The strychnine and cinchonine salts

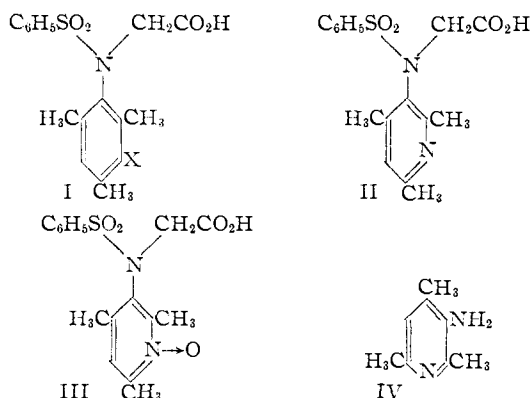
(1) An abstract of a portion of a thesis submitted by Joseph E. Dunbar to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1956; Standard Oil of California Fellow 1954–1955.

(2) R. Adams and K. R. Brower, *THIS JOURNAL*, **78**, 663 (1956).

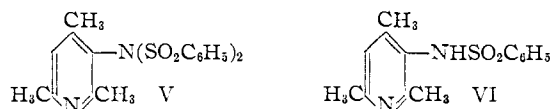
(3) R. Adams and M. Gortatowski, *ibid.*, **79**, 5525 (1957).

were fractionally crystallized but invariably gave fractions of essentially the same specific rotation which upon decomposition failed to yield optically active acids.

The 1-oxide III was then prepared from II, but attempts to resolve it *via* the strychnine salt in acetone also failed.

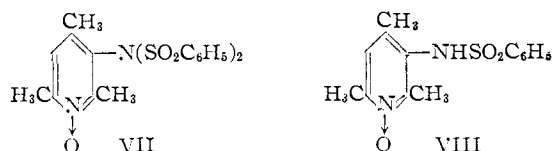


Compound II was synthesized from 3-amino-2,4,6-trimethylpyridine (IV). When a triethylamine solution of IV was treated with an equimolar



quantity of benzenesulfonyl chloride, the amino group reacted with two moles of the chloride, giving N,N-dibenzenesulfonyl-3-amino-2,4,6-trimethylpyridine (V). When two moles of benzenesulfonyl chloride was used V was obtained in 79% yield. Compound V was in turn converted to N-benzenesulfonyl-3-amino-2,4,6-trimethylpyridine (VI) by boiling with sodium ethoxide in ethanol solution. Conversion of VI to N-benzenesulfonyl-N-carbomethoxymethyl-3-amino-2,4,6-trimethylpyridine was accomplished by treatment with methyl bromoacetate and sodium methoxide in methanol. The ester was hydrolyzed to the acid II in dilute hydrochloric acid solution.

The 1-oxides VII and VIII were prepared from the corresponding collidines for use as possible intermediates in synthesis of compound III. However, attempts to replace a benzenesulfonyl group of compound VII with a hydrogen atom to give compound VIII by means of sodium ethoxide gave only oily products which could not be purified. Likewise, treatment of compound VIII with methyl bromoacetate and sodium methoxide failed to give N-benzenesulfonyl-N-carbomethoxymethyl-3-amino-2,4,6-trimethylpyridine 1-oxide (III).



There are no absorption bands in the infrared spectra of pyridine N-oxides that can be assigned with certainty to the N-O bond. Each of the collidine N-oxides reported here, however, could

be differentiated from its corresponding collidine by the absence of the pyridine nitrogen band at 1604 to 1607 cm^{-1} in the infrared spectrum.

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Experimental

All melting points are corrected. The infrared spectra were run in Nujol mulls unless otherwise indicated. A Perkin-Elmer model 21 double beam spectrophotometer was used.

3-Amino-2,4,6-trimethylpyridine.—To a well-stirred mixture of 35.7 g. of 3-nitro-2,4,6-trimethylpyridine⁴ and 10 g. of Raney nickel in 100 ml. of methanol was added a solution of 25 ml. of 85% hydrazine hydrate in 25 ml. of methanol at such a rate that boiling was maintained by the heat of reaction. The addition required about two hours. The reaction mixture was boiled under reflux an additional hour to ensure decomposition of excess hydrazine. The catalyst was then removed by filtration, and the solvent was evaporated *in vacuo*. The residual oil was cooled, and 26.0 g. (89%) of light tan crystals formed. The product was suitable for use without further purification.

N,N-Dibenzenesulfonyl-3-amino-2,4,6-trimethylpyridine.—To a solution of 8.1 g. of 3-amino-2,4,6-trimethylpyridine in 50 ml. of triethylamine was added slowly 21.4 g. of benzenesulfonyl chloride. The mixture became warm and solidified. The mass was warmed for 30 minutes on the steam-bath, cooled and suspended in 150 ml. of water. The crude product, which weighed 19.6 g. (79%), was recrystallized from ethanol to give white needles, m.p. 168°. The infrared spectrum showed no NH bands. The presence of the disulfonamide group was indicated by SO_2 bands at 1177, 1181 and 1386 cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}_2$: C, 57.67; H, 4.84; N, 6.73. Found: C, 57.98; H, 4.81; N, 6.56.

N-Benzenesulfonyl-3-amino-2,4,6-trimethylpyridine.—To an ethanolic solution of sodium ethoxide from 15.3 g. of sodium in 1300 ml. of absolute ethanol, was added 64.9 g. of N,N-dibenzenesulfonyl-3-amino-2,4,6-trimethylpyridine. The resulting mixture was heated under reflux for 2 hours, evaporated to 320 ml. and then diluted to 1500 ml. with distilled water. The pH was adjusted to 6.0 by the addition of dilute hydrochloric acid, and the resulting white precipitate was collected on the filter and dried *in vacuo* over phosphoric anhydride. The crude amide was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°) to give 38.8 g. (90%) of white crystals, m.p. 125.5–126.5°. The infrared spectrum showed the NH band at 3580 cm^{-1} and SO_2 bands at 1340 and 1167 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 60.84; H, 5.84; N, 10.14. Found: C, 60.57; H, 5.60; N, 10.17.

N-Benzenesulfonyl-N-carbomethoxymethyl-3-amino-2,4,6-trimethylpyridine.—To a solution of 39.6 g. of N-benzenesulfonyl-3-amino-2,4,6-trimethylpyridine and 15.6 g. of sodium methoxide in 630 ml. of absolute methanol was added 44.0 g. of freshly distilled methyl bromoacetate. The solution was protected from moisture by a calcium chloride tube in the opening of the condenser. After the solution had been heated under reflux for 48 hours, it was concentrated to 250 ml. and poured into 1500 ml. of ice-water. A light tan gum was formed which crystallized upon standing in the refrigerator for 3 hours. The crystal mass was crushed, collected on a filter, dried and recrystallized (Darco) from ether to give 38.0 g. (76%) of white crystals, m.p. 111–112°.

When the product was recrystallized from methanol-water, benzene-cyclohexane or chloroform-cyclohexane, a different crystal structure was obtained, m.p. 103–103.5°. X-Ray diffraction data confirmed the different crystal structures of the two forms. The infrared spectra of the two forms in chloroform solution were identical; in Nujol mull they were very similar but the product, m.p. 103–103.5°, showed splitting of some of the bands. Both forms hydrolyzed to the same product. Only the 103–103.5° form was

(4) E. Plazek. *Ber.*, **72**, 577 (1939).

analyzed. The infrared spectrum showed the ester C=O band at 1764 cm^{-1} and the C-O band at 1209 cm^{-1} . No NH band was present.

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 58.60; H, 5.78; N, 8.04. Found: C, 58.70; H, 5.71; N, 8.19.

N-Benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine.—A solution of 36.5 g. of N-benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine in 150 ml. of 50% hydrochloric acid was refluxed for 90 minutes. The solution was then evaporated *in vacuo* to dryness on the steam-bath to give the light tan, crystalline hydrochloride, m.p. 243–244°. The hydrochloride was dissolved in a minimum of water, and the resulting solution was treated with Darco. The pH of the solution was adjusted to 5.0 by the addition of about 110 ml. of 2 M aqueous sodium hydroxide. Crystallization of the free acid commenced when the solution was warmed on the hot-plate and was complete after standing at room temperature for an hour. The product weighed 32.9 g. (94%), and upon recrystallization from reagent grade acetone gave fine white crystals, m.p. 211–212° dec. The presence of the C=O band at 1708 cm^{-1} , the C-O band at 1230 cm^{-1} and the OH band at 2400 cm^{-1} in the infrared spectrum indicated the presence of the carboxyl group.

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.67; H, 5.67; N, 8.20.

To a suspension of 0.22 g. of N-benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine was added an ether solution of diazomethane generated from 0.22 g. of N-methylnitrosourea. Evolution of nitrogen was very slow. After 2.5 hours a small portion of unreacted material was removed by filtration, and a few drops of acetic acid was added to the filtrate to destroy excess diazomethane. The ether solution was evaporated to dryness, and the residual oil was triturated with cyclohexane. The resulting solid was twice recrystallized from ether, giving white crystals, m.p. 101–103°. A mixture of this material and an authentic sample of N-benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine gave no depression of melting point.

Attempted Resolution of N-Benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine via the Cinchonine Salt.—Equimolar quantities of N-benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine and cinchonine dissolved in ethyl acetate yielded upon concentration in a stream of dry air several crops of crystals. The first crop, m.p. 175–182° and $[\alpha]^{30\text{D}} +68.2^\circ$ in dimethylformamide, gave upon decomposition an acid which showed zero rotation.

Attempted Resolution of N-Benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine via the Strychnine Salt.—A solution was prepared from 10.00 g. of N-benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine and 10.00 g. of strychnine by boiling in 1700 ml. of water for one hour. Upon cooling in the refrigerator and with subsequent evaporation at room temperature in a stream of air, several crops of crystals were obtained.

A 10-g. portion of the first crop was recrystallized from 825 ml. of boiling water by allowing the solution to stand in the refrigerator for 3 days. White needles were obtained weighing 4.86 g., m.p. 134°. It was prepared for analysis by drying at 65° (1 mm.) for 12 hours; rotation, 0.4998 g. of salt made up to 20.00 ml. with absolute ethanol at 32° gave -0.25° (1 l; $[\alpha]^{25\text{D}} -10.0^\circ$).

Anal. Calcd. for $\text{C}_{27}\text{H}_{40}\text{N}_4\text{O}_6\text{S}$: C, 66.44; H, 6.03; N, 8.38. Found: C, 66.65; H, 5.94; N, 8.35.

A suspension of 1 g. of recrystallized salt in 3 ml. of water was made alkaline by the dropwise addition with stirring of

10% aqueous sodium hydroxide. The precipitated strychnine was removed by filtration, and the filtrate was carefully adjusted to pH 5.0 by the dropwise addition of 2 M hydrochloric acid. The acid crystallized after the reaction mixture had stood at room temperature for a few minutes. The rotation was essentially zero.

N,N-Dibenzene-sulfonyl-3-amino-2,4,6-trimethylpyridine 1-Oxide.—A mixture of 2.00 g. of N,N-dibenzene-sulfonyl-3-amino-2,4,6-trimethylpyridine and 4.00 g. of 30% hydrogen peroxide in 20 ml. of glacial acetic acid was heated for 5 hours at 80–90°. The mixture was neutralized with 9% aqueous sodium bicarbonate. The product crystallized from solution as white platelets, weighing 1.93 g. (93%). Recrystallization from ethanol gave white needles, m.p. 194° dec. The pyridine nitrogen band at 1604 cm^{-1} was absent from the infrared spectrum.

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_5\text{S}_2$: C, 55.54; H, 4.66; N, 6.48. Found: C, 55.63; H, 4.86; N, 6.51.

Conversion of this product to the monobenzenesulfonyl derivative with sodium ethoxide by the general procedure previously described resulted in the formation of an oil which could not be purified.

N-Benzene-sulfonyl-3-amino-2,4,6-trimethylpyridine 1-Oxide.—A solution of 2.00 g. of N-benzene-sulfonyl-3-amino-2,4,6-trimethylpyridine and 4.00 g. of 30% hydrogen peroxide was heated for 3 hours at 80–90°. The mixture was neutralized with 9% aqueous sodium bicarbonate and 1.31 g. (62%) of white solid resulted. The crude product was recrystallized 3 times from aqueous ethanol to give white crystals, m.p. 236° dec. The pyridine nitrogen band at 1607 cm^{-1} was absent from the infrared spectrum.

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_5\text{S}$: C, 57.51; H, 5.52; N, 9.58. Found: C, 57.67; H, 5.52; N, 9.83.

Attempts to introduce the carbomethoxymethyl group by the usual procedure gave an oil which could not be purified.

N-Benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine 1-Oxide.—A solution of 6.00 g. of N-benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine and 20 g. of 30% hydrogen peroxide in 60 ml. of glacial acetic acid was heated at 80–90° for 10 hours. The mixture was evaporated to dryness *in vacuo*. A residue of 4.52 g. (71%) of light tan crystals remained. The crude material was twice recrystallized from a mixture of dry benzene and absolute methanol to give white crystals, m.p. 242–243° dec. The pyridine nitrogen band at 1606 cm^{-1} was absent from the infrared spectrum. Evidence for the carboxyl group was present.

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_5\text{S}$: C, 54.84; H, 5.18; N, 8.00. Found: C, 54.96; H, 5.39; N, 7.63.

Attempted Resolution of N-Benzene-sulfonyl-N-carboxymethyl-3-amino-2,4,6-trimethylpyridine 1-Oxide via the Strychnine Salt.—The strychnine salt was prepared by boiling in reagent acetone. After evaporation of the solution to small volume and cooling in the refrigerator for 20 days, crystals, m.p. 206–226°, $[\alpha]^{30\text{D}} -72.2^\circ$, resulted. Several recrystallizations from acetone gave a product, $[\alpha]^{29\text{D}} -75.0^\circ$. When the last product was dissolved in acetone, and crystallization was allowed to take place over a period of 19 days, two forms of crystals were obtained: (A) large, tetragonal crystals and (B) small needles. The two forms were mechanically separated; A melted at 216–247°, $[\alpha]^{24\text{D}} -128^\circ$, and B at 214–220°, $[\alpha]^{22\text{D}} -61.0^\circ$. Fraction B on decomposition with alkali gave an acid with the same melting point as the racemic form and with zero rotation. Fraction A was subjected to the same decomposition, but no acid was obtained.

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