(2) *4-Aminobenzenesulfonylhydrazone of salicylaldehyde.* Seven and five-tenths grams (0.040 mole) of 4-aminobenzenesulfonylhydrazine were dissolved in a hot solution composed of 50 ml. of methanol and 50 ml. of water. To the above solution were added with stirring, 6.1 g. (0.040 mole) of salicylaldehyde. The mixture developed an orange-yellow color and became almost homogeneous. Shortly thereafter yellow-orange crystals began to precipitate from the reaction mixture. The separation of the product was facilitated by the dilution of the reaction mixture with water. The crystals were collected on a suction filter and air dried. The product weighed 11.6 g. (quantitative yield) and melted with decomposition at 167–168°.

The product was recrystallized two times from equal volumes of methanol and water. The yellow crystals weighed 5.6 g. (47% yield) and melted with decomposition at 176.5–177°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42. Found: C, 53.71; H, 4.60; N, 14.36.

(3) *4-Nitrobenzenesulfonylhydrazone of propiophenone.* Seven and four-tenths grams (0.034 mole) of 4-nitrobenzenesulfonylhydrazine were dissolved in 100 ml. of hot methanol containing a little water. Four grams (0.030 mole) of propiophenone were then added dropwise with stirring. Yellow crystals separated from the reaction mixture as it cooled to room temperature. After 2 hr. at room temperature the crystals were collected on a suction filter and dried in a 95° oven. The yellow crystals weighed 9.8 g. (98% yield) and melted with decomposition at 147–150°.

The product was recrystallized from methanol containing a little water. The pale yellow crystals weighed 8.1 g. (81% yield) and melted with decomposition at 150–152°.

Anal. Calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.04; H, 4.35; N, 12.41.

(4) *4-Acetamidobenzenesulfonylhydrazone of 2-acetyl-1-hydroxynaphthalene.* In a mortar 1.86 g. (0.01 mole) of 2-acetyl-1-hydroxynaphthalene and 2.3 g. (0.01 mole) of 4-acetamidobenzenesulfonylhydrazine were thoroughly mixed. After transferring to a large wide-diameter test tube the contents then were heated to 125° (oil bath). At this temperature the mixture liquefied somewhat and water evaporated; after 15 min., 5 ml. of glacial acetic acid and 2 drops concentrated sulfuric acid together with 15 ml. absolute ethanol were added and the mixture refluxed. After about 1 hr. everything went into solution. Shortly after this a yellow precipitate began to appear, after 1 additional hr. of refluxing, the contents were poured on ice, and washed with alcohol and ether. Yield 2.4 g.

The compound was extremely insoluble in all common solvents. Therefore, the analytical sample was extracted with boiling alcohol.

Anal. Calcd. for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82; N, 10.57. Found: C, 60.23; H, 4.88; N, 10.71.

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[CONTRIBUTION FROM THE CITRUS EXPERIMENT STATION OF THE UNIVERSITY OF FLORIDA]

Derivatives of (+)-Limonene. II. 2-Amino-1-*p*-menthanols[1]

WILLIAM F. NEWHALL

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Several new aminoalcohols including 2-amino-1-*p*-menthanol have been synthesized from (+)-limonene. Partial hydrogenation of (+)-limonene followed by oxidation with peracetic acid affords *p*-menthane-1,2-epoxide. The epoxide ring is readily opened by ammonia and amines to give derivatives of 2-amino-1-*p*-menthanol. The direction of ring opening in *p*-menthane-1,2-epoxide and the configurations of the two *trans* isomers of 2-amino-1-*p*-menthanol isolated have been established by an independent synthesis from *trans*-*p*-menthane-1,2-diol of known configuration.

A number of new 2-amino-1-*p*-menthanols have been synthesized from (+)-limonene in connection with a study of limonene derivatives having possible physiological activity.

Hydrogenation of (+)-limonene[2] without solvent, at low pressure, over a 5% platinum on Darco G-60 catalyst proceeds smoothly to afford Δ^1-*p*-menthene (I) in virtually quantitative yield. The details of this hydrogenation have been presented in a previous publication.[3] This ease of partial hydrogenation of (+)-limonene was first described by Vavon[4] and has since been utilized by a number of other authors[5,6] to prepare Δ^1-*p*-menthene (I).

Treatment of (I) with perbenzoic acid in anhydrous chloroform at 10° according to the method of Pigulevskii and Kozhin[6] affords *p*-menthane-1,2 epoxide (II) in 80% yield. Royals[7] has recently reported the preparation of (II) by hydrogenation of (+)-limonene epoxide over Adams' catalyst. Because of the difficulties inherent in the preparation of large quantities of (II) by perbenzoic acid

(1) Florida Agricultural Experiment Stations Journal Series, No. 898.

(2) Samples of citrus D-limonene were supplied by Kuder Citrus Pulp Co., Lake Alfred, Fla.

(3) W. F. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).

(4) M. G. Vavon, *Bull. soc. chim. IV*, **15**, 282 (1914).

(5) K. Fujita and T. Matsuura, *J. Sci. Hiroshima Univ.*, **18A**, 455 (1955).

(6) G. V. Pigulevskii and S. A. Kozhin, *Zhur. Obshchei Khim.*, **27**, 803 (1957).

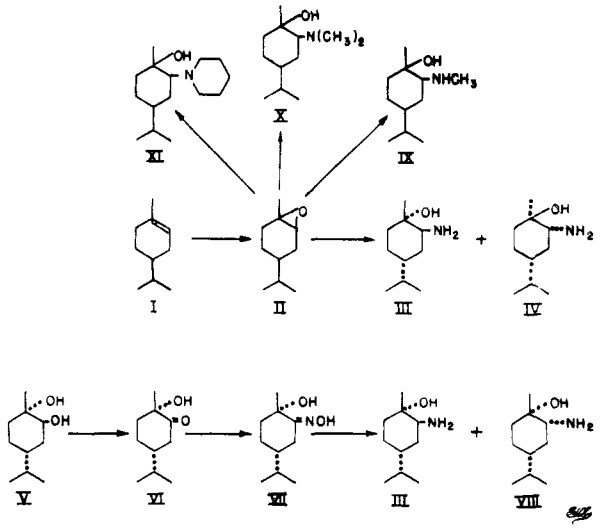
(7) E. Earl Royals, paper no. 92, Southeastern Regional Meeting of American Chemical Society, December 1958.

oxidation, an alternate procedure was sought employing commercially available 40% peracetic acid as the epoxidizing agent. Terry and Wheeler[8] have shown that the epoxidation of natural oils can be conducted in the two-phase system which results when the oils are stirred with aqueous peracetic acid solutions. The *in situ* epoxidations discussed by Gall and Greenspan[9] were also conducted in a two-phase system maintained by using a large amount of water along with a hydrocarbon diluent. It was found that the epoxidation of (I) can be accomplished in a similar manner. The free sulfuric acid in the peracetic acid is neutralized with sodium acetate and the epoxidation performed at room temperature. Sufficient water and benzene are added to keep the reaction mixture two-phase at all times. Using this procedure, a 60% yield of (II) has been obtained after a reaction time of 1.5 hours.

By heating at 135–140° for 24 hours in a sealed tube with excess aqueous ammonia solution, (II) is converted to a mixture of two *trans* aminomenthanols (III) and (IV). It is well known that the overall result of oxide formation and cleavage is equivalent to *trans* addition.[10] Both (III) and (IV) are represented as *trans* isomers of 2-amino-1-*p*-menthanol from analogy with the work of Royals,[7] who has shown that the cleavage of (II) by ethyl alcohol under the influence of basic catalysts yields exclusively 2-ethoxy-1-*p*-menthanol. The configuration of (III) has been established by an independent synthesis and therefore it is reasonable to assign configuration (IV) to the other isomer isolated.

The formation of (III) and (IV) is possible only if the epoxide (II) is a mixture of isomers, one with the oxygen on the same side of the ring and the other with the oxygen on the opposite side of the ring as the isopropyl group. This is analogous to the known formation of two *trans*-*p*-menthane-1,2-diols from the hydroxylation of Δ^1-*p*-menthene[3,11] (I). The mixed *trans* isomers of 2-methylamino-1-*p*-menthanol (IX), 2-dimethylamino-1-*p*-menthanol (X) and 2-piperidyl-1-*p*-menthanol (XI) are prepared in a similar manner by reaction of (II) with aqueous methylamine, aqueous dimethylamine, and piperidine respectively. All of these aminoalcohols are high boiling, colorless, slightly viscous liquids which are strong bases only slightly soluble in water.

In order to establish that the direction of cleavage of the oxide ring in (II) does proceed, as shown, to give derivatives of 1-*p*-menthanol, isomer (III)



of 2-amino-1-*p*-menthanol has been synthesized from *trans*-*p*-menthane-1,2-diol (V). The configuration of (V) is known[3] from the reported work of Jefferies and Milligan[11] and Cole and Jefferies[12] on the racemic *trans*-*p*-menthane-1,2-diols. Tertiary butyl chromate[13] oxidation of (V), according to the procedure of Linder and Greenspan,[14] gives the liquid ketol (VI) which is converted by conventional means to the crystalline hydroxyoxime (VII). Hydrogenation of (VII) at low pressure over Raney nickel catalyst affords a mixture of the two isomers of 2-amino-1-*p*-menthanol (III) and (VIII) predicted from the two possible orientations of the amino group. This mixture is separated by fractional crystallization of the amine picrates into two picrates, which both form crystalline hydrates. One hydrate melts at 69–73° and is converted by vacuum drying at 85° to a crystalline, anhydrous picrate melting at 132°. The other hydrate crystallizes as yellow needles, m.p. 85–95°, and is converted by vacuum drying at 64° to an amorphous glass. The aminoalcohol regenerated from this amorphous picrate is a pure, crystalline compound melting at 79.4–80.0°.

The liquid mixture of trans-2-amino-1-*p*-menthanols (III) and (IV) on treatment with picric acid also affords two crystalline amine picrates. One crystallizes as an anhydrous picrate melting at 187°, while the other crystallizes as a hydrate (m.p. 71–74°) which, on drying, affords an anhydrous picrate melting at 132°. The latter picrate is identical in all respects, including infrared absorption, to the picrate melting at 132° synthesized from (V) above.

(8) D. E. Terry and D. H. Wheeler, U. S. Patent **2,458,484** (to General Mills, Inc.) Jan. 4, 1949.

(9) R. J. Gall and F. P. Greenspan, *Ind. Eng. Chem.*, **47**, 147 (1955).

(10) *Organic Chemistry*, Fieser and Fieser, second ed., D. C. Heath and Company, 1950, p. 287.

(11) P R. Jefferies and B. Milligan, *J. Chem. Soc.*, 4384 (1956).

(12) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956).

(13) R. V. Oppenauer and H. Oberrauch, *Anales asoc. quim argentina*, **37**, 246 (1949).

(14) S. M. Linder and F. P. Greenspan, *J. Org. Chem.*, **22**, 949 (1957).

This establishes the configuration of the parent aminoalcohol from the picrate melting at 132° as (III) since the formation of (III) is predicted from each of the two reaction schemes. The aminoalcohol corresponding to the amorphous picrate (hydrate m.p. 95°) must then have the configuration of (VIII). If cleavage of (II) is assumed to proceed exclusively in one direction,[7] (IV) must represent the configuration of the aminoalcohol from the picrate melting at 187°. In contrast to the *cis* aminoalcohol (VIII) which, as mentioned previously, is a crystalline solid, the two *trans* isomers (III) and (IV) are liquids.

EXPERIMENTAL

All melting points reported are uncorrected.

p-Menthane-1,2-epoxide (II). Six grams of sodium acetate was added with stirring to a solution of 100 ml. of 43% peracetic acid (0.566 moles) in 300 ml. of water at 25°. A solution of 70 g. (0.507 moles) of Δ^1-*p*-menthene (I) in 200 ml. of benzene was added rapidly and the resulting mixture was stirred and cooled to maintain a temperature of 22–24° for 1.5 hr. The benzene layer was then separated, washed 5 times with water, once with sodium bisulfite, once with sodium carbonate solution, and again with water until neutral. After drying over anhydrous sodium sulfate, the benzene was removed under vacuum at 40° and the residual liquid was distilled. At 69–70° (5.0 mm.) 46.8 g. (60%) of colorless liquid was collected. This product is sufficiently pure for use directly in the preparation of 2-amino-1-*p*-menthanols. Redistillation to remove traces of Δ^1-*p*-menthene (I) gave 42.3 g. (54%) of *p*-menthane-1,2-epoxide (II), which distilled at 66.0–66.3 (5.2 mm.), n_D^{23} 1.4493; $[\alpha]_D^{23}$ +57.88 (reported,[6] b.p. 66.5–66.7°/7 mm.; n_D^{23} 1.4509; $[\alpha]_D^{20}$ +57.53).

2-Amino-1-p-menthanols (III) *and* (IV). Two sealed glass tubes each containing 14.5 g. of *p*-menthane-1,2-epoxide (II) and 24 ml. of aqueous ammonium hydroxide (28%) were heated at 135–140° for 24 hr. The cooled tubes were then opened, the contents combined and extracted once with benzene. The benzene layer was separated, dried over anhydrous sodium sulfate and the benzene removed under reduced pressure (40°). Distillation of the residual oil gave 23.2 g. (75%) of colorless, viscous, mixed *trans*-2-amino-1-*p*-menthanols (III) and (IV), b.p. 95–100° (1.5 mm.). Redistillation afforded material boiling at 100–101° (1.6 mm.). n_D^{23} 1.4853, $[\alpha]_D^{23}$ +39.

Anal. Calcd. for $C_{10}H_{21}ON$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.10; H, 12.18; N, 8.33.

Twenty-four grams of the mixed *trans*-2-amino-1-*p*-menthanols (III) and (IV) (b.p. 95–100°/1.5 mm.) was fractionally distilled through an 18-inch Vigreux column at 0.95 mm. and separated into three crude fractions. Each of the three fractions was treated with excess picric acid in methanol. After removal of the methanol under vacuum, the picrates were crystallized from water. After several recrystallizations from water, pale yellow needles, m.p. 69–73°, were obtained from fraction (1). After drying under vacuum at 85°, these crystals lost water of hydration and recrystallized to afford the picrate of (III), m.p. 130–132°.

Anal. Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.54; H, 5.84; N, 13.82.

The free aminoalcohol (III) was not regenerated from its picrate.

Yellow needles of the picrate of (IV) were obtained from fraction (3). After several recrystallizations from water, a sample melting at 184–187° was obtained.

Anal. Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 48.31; H, 5.95; N, 13.65.

The free aminoalcohol (IV) was not regenerated from its picrate. Fraction (2) contained a mixture of the two picrates isolated from fractions (1) and (3).

2-Methylamino-1-p-menthanols (IX). Reaction of *p*-menthane-1,2-epoxide (II) with aqueous methyl amine (30%), using the same amounts of reactants and reaction conditions identical to those described for the preparation of the 2-amino-1-*p*-menthanols (III) and (IV), gave a liquid product which was vacuum distilled. At 101–107° (2.0 mm.), 25.6 g. (74%) of the mixed *trans* isomers of 2-methylamino-1-*p*-menthanol (IX) distilled as a colorless viscous oil. Redistillation afforded material boiling at 94–97° (1.5 mm.). n_D^{20} 1.4790, $[\alpha]_D^{23}$ +44.

Anal. Calcd. for $C_{11}H_{23}ON$: C, 71.29; H, 12.51; N, 7.56. Found: C, 71.04; H, 12.21; N, 7.59.

2-Dimethylamino-1-p-menthanols (X). Reaction of *p*-menthane-1,2-epoxide (II) with aqueous dimethyl amine (25%), using the same amounts of reactants and reaction conditions identical to those described for the preparation of the 2-amino-1-*p*-menthanols (III) and (IV), gave a liquid product which was vacuum distilled. At 103–108° (2.5 mm.), 25.3 g. (68%) of the mixed *trans* isomers of 2-dimethylamino-1-*p*-menthanol (X) distilled as a colorless, fluid oil. Redistillation afforded material boiling at 90–95° (1.4 mm.). n_D^{23} 1.4722, $[\alpha]_D^{23}$ +36.

Anal. Calcd. for $C_{12}H_{25}ON$: C, 72.30; H, 12.64; N, 7.03. Found: C, 71.81; H, 12.57; N, 6.98.

2-Piperidyl-1-p-menthanols (XI). The preparation of (XI) required more drastic conditions than that of any of the other 2-amino-1-*p*-menthanols. Two sealed glass tubes were prepared, each containing 14.5 g. of *p*-menthane-1,2-epoxide (II) and 15 ml. of piperidine. This mixture is homogeneous in contrast to the two-phase systems resulting from admixture of (II) with aqueous bases. After heating at 145–150° for 72 hr., the cooled tubes were opened, most of the piperidine was removed at reduced pressure (50°) and the residual oil was distilled under vacuum. At 69–71° (5.1 mm.) 13.4 g. of unchanged (II) was recovered (n_D^{23} 1.4489). A mixture of the trans-2-piperidyl-1-*p*-menthanols (XI) (14.5 g.) distilled at 126–130° (1.6 mm.) as a pale yellow oil. This represents a conversion yield to (XI) of 61%. Redistillation afforded material boiling at 126–129° (1.6 mm.). n_D^{23} 1.4872, $[\alpha]_D^{23}$ +39.

Anal. Calcd. for $C_{15}H_{29}ON$: C, 75.25; H, 12.21; N, 5.85. Found: C, 75.67; H, 11.94; N, 5.95.

2-Keto-1-p-menthanol (VI). *tert*-Butyl chromate was prepared by adding 29.5 g. of chromium trioxide in small portions to 84 ml. of *tert*-butyl alcohol with slight cooling. A solution of 49.3 g. of *trans*-*p*-menthane-1,2-diol (V) in 400 ml. of benzene was added dropwise to the oxidant while stirring and cooling the solution to maintain a temperature of 25–28°. The mixture was stirred for a total reaction time of 2 hr. at the same temperature. The complex was hydrolyzed by the addition in succession of 300 ml. of water, 60 g. of hydrated oxalic acid, and 300 ml. of 20% sulfuric acid with stirring. After 3 hr. the benzene layer was separated, washed once with sodium carbonate solution and dried over anhydrous sodium sulfate. After removal of the benzene at reduced pressure, the residual oil was distilled under vacuum. At 90–94° (1.4 mm.), 17.4 g. (36%) of colorless, slightly viscous oil was collected. Redistillation afforded material boiling at 88° (1.3 mm.). n_D^{23} 1.4647, $[\alpha]_D^{23}$ +9.8.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 69.70; H, 10.20.

2-Keto-1-p-menthanol oxime (VII). Seventeen grams of 2-keto-1-*p*-menthanol (VI) was warmed for a few minutes in an aqueous alcoholic solution containing 50 g. of hydroxylamine hydrochloride and 20 g. of sodium hydroxide. On cooling, colorless platelets of oxime (VII) separated from solution. These crystals weighed 12.6 g. (68%) and melted at 104–105°. Several recrystallizations from benzene–petroleum ether (30–60°) solution afforded colorless prisms, $[\alpha]_D^{23}$ +95.69 (10% acetone solution) m.p. 105–106°.

Anal. Calcd. for $C_{10}H_{19}O_2N$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.75; H, 10.50; N, 7.70.

2-Amino-1-p-menthanols (III) *and* (VIII). Two teaspoons of Raney nickel catalyst were added to a solution of 20 g. of (VII) in 150 ml. of methanol and hydrogenation was carried out at 50 p.s.i. at 65°. Ninety-three % of the theoretical volume of hydrogen calculated for 2 moles was taken up in 70 min. The catalyst was removed by filtration and about one half of the methanol was evaporated from the filtrate at reduced pressure. Excess picric acid was added together with enough water to make the solution saturated at the boiling point. A picrate crystallized from the cooled solution as yellow needles, m.p. 88–94°, 22.6 g. [47% from (VII)]. This melting point was not improved after repeated recrystallizations from water. During vacuum drying at 64°, this picrate lost water of hydration and became an amorphous glass.

Anal. Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.47; H, 5.91; N, 13.95.

The *cis* isomer of 2-amino-1-*p*-menthanol (VIII) was regenerated from the hydrated picrate (m.p. 88–94°) by treatment with dilute aqueous sodium hydroxide followed by ether extraction. Evaporation of the ether afforded colorless needles which were purified by vacuum sublimation. The sublimed material melted at 79.4–80.0°, $[\alpha]_D^{23}$ −97.72 (10% acetone solution).

Anal. Calcd. for $C_{10}H_{21}ON$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.85; H, 11.86; N, 8.26.

The filtrate from the above picrate (m.p. 88–94°) was evaporated to dryness under vacuum and the residue dissolved in water. A crystalline picrate m.p. 63–72° (10.4 g.) [21.7% from (VII)] separated slowly from the cooled solution. Several recrystallizations from water afforded pale yellow needles, m.p. 71–74°. After drying under vacuum at 85°, these crystals lost water of hydration and recrystallized to give the picrate of III, m.p. 130–132°. A mixture of this picrate with the picrate (m.p. 130–132°) prepared from (II) showed no melting point depression.

LAKE ALFRED, FLA.

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

The Preparation and Bacteriostatic Activity of Substituted *m*-Nitrocarbanilides

D. J. BEAVER, D. P. ROMAN, AND P. J. STOFFEL

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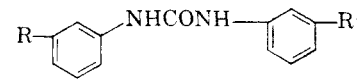
The preparation and *in vitro* bacteriostatic activity of some substituted *m*-nitrocarbanilides against *Staphylococcus aureus* are described. A discussion of specific activity as related to chemical structure is included.

The present paper is a continuation of work described previously[1,2] interrelating chemical structure with bacteriostatic activity. The remarkable specificity encountered in the tri- and tetra-chlorocarbanilides[3] has now been duplicated in the substituted nitrocarbanilides. In both cases, antimicrobial activity was enhanced or completely lost with slight modifications in chemical structure. The more effective nitrocarbanilides completely inhibited the growth of *Staphylococcus aureus* (SA) in dilutions of one to ten million.

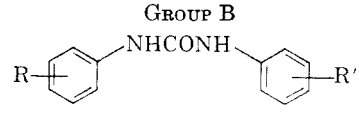
In the course of screening the carbanilides reported in this paper it was soon apparent that the substituted nitrocarbanilides were as specific in their structural requirements to obtain bacteriostatic activity as was found previously for the trichlorocarbanilides.[3] The 3-nitrocarbanilides were found to be inactive unless substituted with a halogen in the 3 position of the second phenyl ring when the maximum activity at a dilution of one part to ten million parts was obtained. The presence of either the nitro or the halogen in positions other than the 3 position completely inactivated the compounds. These data are shown in groups A and B. (The compounds are numbered consecutively for ready cross reference to Table I where their physical properties are listed)

GROUP A



No.	R	R'	SA[4]
4	Chloro	Chloro	0
8	Nitro	Nitro	0
6	Nitro	Chloro	10 Million

GROUP B



No.	R	R'	SA
24	2-Nitro	2-Nitro	0
5	2-Nitro	4-Chloro	0
23	3-Nitro	2-Nitro	0
35	3-Nitro	2-Methyl-5-nitro	0
7	3-Nitro	4-Chloro	0
34	4-Nitro	4-Nitro	0
1	4-Nitro	3-4-Dichloro	0
2	2-Nitro	3,4-Dichloro	0

(1) D. J. Beaver and P. J. Stoffel, *J. Am. Chem. Soc.*, **74**, 3410 (1952).

(2) D. J. Beaver, R. S. Shumard, and P. J. Stoffel, *J. Am. Chem. Soc.*, **75**, 5579 (1953).

(3) D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957).

(4) In groups A–F, the figures under "SA" refer to the maximum dilution which will completely inhibit the growth *in vitro* of the organism *Staphylococcus aureus*. The bacteriostatic test procedure is described in ref. (3).