Synthesis of the Lactone (XII). Condensation of *l*-Camphenilone with Methyl Propiolate.—A solution of *l*-camphenilone[19] (2.5 g.), m.p. 37°, $[\alpha]^{22}D$ −12.23° (*l* 1 dm.; *c* 6.946, benzene), and methyl propiolate[20] (1.68 g.) in absolute ether (30 ml.) was gradually added to a greyish suspension, prepared from ferric nitrate (100 mg.), liquid ammonia (500 ml.), and sodium (0.45 g.) under anhydrous conditions, with mechanical stirring in about 1 hr. The stirring was continued for another 2 hr. and the mixture was allowed to stand at room temperature overnight, during which time almost all the ammonia had evaporated. The mixture was treated with water (300 ml.). Extraction with ether (150 ml.) gave only a small amount of a neutral material which gave, on saponification with 10% alcoholic alkali, an acidic product (0.10 g.) and unchanged camphenilone (0.8 g.). The alkaline solution from the condensation was acidified with dilute hydrochloric acid and the liberated acid (1.87 g.) was isolated by extraction with ether (350 ml.). The two acidic portions were combined. Yield, 1.97 g. It is a viscous gum.

Catalytic Reduction of the Acid (XI).—A mixture of the acid (1.96 g.), platinic oxide (100 mg.), and 96% methanol (50 ml.) was shaken with hydrogen at room temperature under 20 atmospheric pressure[21] for 4 hr. The methanolic solution, left after filtering off the catalyst, gave, on removal of the solvent, a solid (1.5 g.), m.p. *ca.* 95°, which was probably the expected lactone mixed with some impurity. It was, therefore, refluxed with 10% alcoholic potassium hydroxide (35 ml.) for 3 hr. The alcohol was distilled and the alkaline solution diluted with water (50 ml.) and then extracted with ether (100 ml.). The ether extract gave a small amount (0.05 g.) of a gummy product with a camphoraceous smell. The alkaline solution was acidified under ice-cooling with dilute hydrochloric acid, and the organic matter taken up in ether (100 ml.); the ether extract was shaken with 5% sodium carbonate solution (50 ml.). The neutral ether extract gave the lactone (0.45 g.), m.p., 98–100°. The sodium carbonate extract was acidified and the liberated material (0.72 g.) heated with acetic anhydride (5 ml.) on the steam bath for 1 hr. The residue left on removal of the acetic anhydride at *ca.* 110°/50 mm. was boiled with water (10 ml.) for 1 hr. and the product (0.60 g.) was extracted with ether, m.p., 98–100°. The two samples were combined and the mixture (1.05 g., 57.3%) gave, on crystallizing twice from petroleum ether, shiny white plates, m.p., 103–104°, $[\alpha]^{21}D$ −5.6 (alcohol, *c* 4.642; *l* 0.5 dm., α, 0–130°) identical in melting point, mixed melting point and infrared spectrum with the lactone of tricycloekasantalic acid.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.22; H, 9.27. Found: C, 74.77; H, 9.22.

The synthetic lactone (1 g.) gave, on treatment with methanolic hydrogen chloride, a chloro ester (1.28 g.) which, upon dehydrochlorination with dimethylaniline (as described previously in the case of the lactone of tricyclosantalic acid), furnished an unsaturated ester (1.04 g.) which gave, upon distillation, a colorless liquid (0.869 g.), b.p. 93°/1 mm., n^{22} 1.4800; d^{22}_4 1.002 $[\alpha]^{22}D$ −9.38° (pure oil, *l* 0.5 dm.).

Anal. Calcd. for $C_{13}H_{20}O_2/\overline{1}$: C, 75.00; H, 9.61; M_R, 59.02. Found: C, 75.51; H, 9.70; M_R, 59.33.

The above ester gave, on hydrolysis, an acid,[22] m.p. 105–106°, undepressed on admixture with the corresponding acid from the lactone of tricycloekasantalic acid.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.22; H, 9.27; equiv. wt., 194. Found: C, 73.80; H, 9.27; equiv. wt., 195.

This acid gave the lactone on refluxing with dilute sulfuric acid. Hence, the behavior of the synthetic lactone is similar to that of the lactone from tricycloekasantalic acid.

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(19) It was prepared from *l*-camphene, $[\alpha]^{22}D$ −15.2° (petroleum ether; *c* 6.000; *l* 1 dm., m.p. 48°), by treating it with nitrogen tetroxide (*cf.* Cohen and Calvert, *J. Chem. Soc., Trans.*, **71**, 1052 (1891)) and then decomposing the resultant product with alcoholic potassium hydroxide (*cf.* W. Hückel, *Ann.*, **549**, 186 (1941) and papers cited there).

(20) Prepared by using the experimental conditions of C. K. Ingold, *J. Chem. Soc., Trans.*, **127**, 1202 (1925).

(21) The uptake of hydrogen at the ordinary pressure was found to be very slow.

(22) Compare the preparation of this acid by G. Longlois, *Ann. Chem.* [9] **12**, 290 (1919), Elsevier's "Encyclopedia of Org. Chem.," **12A**, 624.

Bromochlorovanillins: Some Substitution Reactions

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The previously unreported monobromomonochlorovanillins and dibromomonochloro- and monobromodichlorovanillins have been prepared. Some direct substitution reactions with related molecules have been accomplished under conditions which are more favorable for these changes than those which had been employed earlier.

The objectives of this study involved the preparation of previously unreported bromochloro derivatives of vanillin and information concerning ease of bromination or chlorination of certain substituted vanillins and vanillin derivatives.

Of the six possible monobromomonochlorovanillins, all but 2-bromo-6-chloro- and 6-bromo-2-chlorovanillin have been reported,[1,2] but of the six possible dibromomonochloro- and monobromodichlorovanillins, only 5-bromo-2,6-dichlorovanillin[1] has been described. The preparations in this work include the remaining possibilities: the two monobromomonochlorovanillins named above, 2,5-dibromo-6-chloro-, 5,6-dibromo-2-chloro-, 2,6-dibromo-5-chloro-, 6-bromo-2,5-dichloro-, and 2-

(1) L. C. Raiford and J. G. Lichty, *J. Am. Chem. Soc.*, **52**, 4576 (1930).

(2) 2-Bromo-5-chlorovanillin (m.p. 175–176°) has been prepared (D. E. Floyd, thesis, State University of Iowa, 1943) from 2-amino-5-chlorovanillin[1] in 75% yield by a Sandmeyer reaction.

bromo-5,6-dichlorovanillin. Several new intermediates were prepared in the course of these experiments, and the work in connection with these compounds is described also.

2-Bromo-6-chlorovanillin was obtained from 2-amino-6-chlorovanillin[1] by a Sandmeyer reaction. For the preparation of 6-bromo-2-chlorovanillin, 6-bromovanillin acetate[3] was nitrated, the acetyl group was removed, 6-bromo-2-nitrovanillin was reduced, and the amino group was replaced by chlorine by a Sandmeyer reaction.

2,5-Dibromo-6-chlorovanillin was obtained by two procedures. Direct bromination of 2-bromo-6-chlorovanillin gave the desired compound, but the yield was not high. In another sequence, 6-chloro-2-nitrovanillin[1] was brominated readily in the 5 position, and the nitro compound was reduced to 2-amino-5-bromo-6-chlorovanillin; this amino compound was prepared also by the bromination of 2-amino-6-chlorovanillin.[1] (That the amino group was in the position indicated was demonstrated by converting the aminobromochloro compound to 5-bromo-6-chlorovanillin.[1]) From 2-amino-5-bromo-6-chlorovanillin, 2,5-dibromo-6-chlorovanillin was obtained by a Sandmeyer reaction.

5,6-Dibromo-2-chlorovanillin was prepared easily by direct bromination of 6-bromo-2-chlorovanillin.

2-Amino-6-bromovanillin[4] was acetylated, and the acetamino compound was chlorinated in the 5 position; from 2-acetamino-6-bromo-5-chlorovanillin, 6-bromo-2,5-dichlorovanillin was obtained by hydrolysis of the amide linkage followed by a Sandmeyer replacement of the amino group by chlorine. 2-Amino-6-bromo-5-chlorovanillin was prepared also by converting 6-bromovanillin acetate to 6-bromo-2-nitrovanillin,[4] which was chlorinated to the 5-chloro compound; this when reduced gave the amino compound named. (That the amino group was in the 2 position was shown by removing it and obtaining 6-bromo-5-chlorovanillin.[1]) Direct chlorination of 6-bromo-2-chlorovanillin also gave 6-bromo-2,5-dichlorovanillin.

Two procedures were followed for the preparation of 2,6-dibromo-5-chlorovanillin. One involved a Sandmeyer replacement of the amino group in 2-amino-6-bromo-5-chlorovanillin by bromine; the other was a direct chlorination of 2,6-dibromovanillin.[4]

2-Amino-6-chlorovanillin[1] was the starting material for one preparation of 2-bromo-5,6-dichlorovanillin; the acetamino compound was made and chlorinated; 2-acetamino-5,6-dichlorovanillin was then hydrolyzed to the amino compound. 2-Amino-5,6-dichlorovanillin was prepared also from 6-chloro-2-nitrovanillin[1] by direct chlorination followed by reduction. Sandmeyer replacement of the amino group by bromine gave 2-bromo-5,6-dichlorovanillin. This was obtained also by direct chlorination of 2-bromo-6-chlorovanillin.

The direct bromination of 2-bromo-6-chlorovanillin resulted in substitution at position 5; although the yield was not high (30%), the principal directive influences appear to operate as would be expected normally. Similarly, bromination of 6-chloro-2-nitrovanillin and 2-amino-6-chlorovanillin gave the expected 5-bromo substitution products (high yields).

When 6-bromo-2-chlorovanillin was brominated, the yield of the 5-bromo substitution product was higher (86%) than when the 2-bromo-6-chloro compound was brominated (30%); this result is different from what would be expected if the size of the halogen atom in position 6 were to influence the substitution sterically.

5,6-Dibromo-2-nitrovanillin was obtained easily (97% yield) from 6-bromo-2-nitrovanillin by direct bromination, but chlorination of some 2,6-disubstituted vanillins is difficult to accomplish. However, the use of an iodine–ferric chloride catalyst[5] resulted in substitution of chlorine at position 5 in 6-bromo-2-nitrovanillin, in 6-bromo-2-chlorovanillin, in 2,6-dibromovanillin, in 6-chloro-2-nitrovanillin, and in 2-bromo-6-chlorovanillin.

The special effectiveness of the iodine–ferric chloride mixture in chlorinations is illustrated further by some experiments with 6-chlorovanillin. Direct chlorination was not realized in chloroform, glacial acetic acid, or pyridine solutions with iodine as catalyst; but a good yield of 5,6-dichlorovanillin was obtained by chlorination of 6-chlorovanillin in glacial acetic acid solution with an iodine–ferric chloride mixture as catalyst.

In contrast to the difficulties encountered when chlorination of 6-chlorovanillin was attempted, 5,6-dibromovanillin was obtained readily from 6-bromovanillin by direct substitution in glacial acetic acid solution with iodine as catalyst. Here again, neither the larger substitutent (bromine) in position 6 nor the larger entering unit (bromine) appears to exert significant steric inhibition; had such been involved, bromination of the 6-bromo compound should have been more difficult than chlorination of the analogous 6-chloro compound.

In another series of experiments also, difficulties were encountered when efforts were made to introduce chlorine. Several sets of conditions were used in attempts to prepare 5-chloro-2-nitrovanillin from the 2-nitro compound. Most of these resulted only in recovery of starting material, but the desired product was obtained by the action of chlorine in chloroform solution with iodine as catalyst.

Although 5-chlorovanillin triacetate may be chlorinated rather easily in position 6, attempted

(3) L. C. Raiford and W. C. Stoesser [*J. Am. Chem. Soc.*, **49**, 1077 (1927)] prepared this compound, but there was no report of melting point or analysis.

(4) L. C. Raiford and W. C. Stoesser, *J. Am. Chem. Soc.*, **50**, 2556 (1928).

(5) H. E. Fierz-David [*Naturwissenschaften*, **17**, 13 (1929)] reported unusual effectiveness of mixtures of iron and iodine in facilitating chlorinations.

bromination (even at higher temperature) resulted in recovery of starting material. Because directive influences of the substituents on the ring should be the same in each of these instances, the failure of bromine to yield readily an electrophilic substitution product may be attributable to the larger size of the attacking unit.

Details of the laboratory work are presented in the Experimental.

Experimental

2-Bromo-6-chlorovanillin.—A 6-g. quantity (0.0298 mole) of 2-amino-6-chlorovanillin[1] (from: vanillin; vanillin triacetate; 6-chlorovanillin triacetate; 6-chloro-2-nitrovanillin acetate; 6-chloro-2-nitrovanillin; 2-amino-6-chlorovanillin) was dissolved in 25 ml. of 85% sulfuric acid, the solution was cooled to 0°, 2.8 g. (0.04 mole) of sodium nitrite was added in small portions, and 3 g. of freshly prepared cuprous bromide in 20 ml. of 40% hydrobromic acid was introduced. The mixture was allowed to warm slowly to room temperature, heated on a steam bath for 2 hr., and cooled. The solid was collected by filtration and crystallized from 40% ethanol; the product, pale yellow needles, weighed 4.99 g. (0.0188 mole, 63% yield); m.p. 169.5–170.5°.

Anal. Calcd. for $C_8H_6BrClO_3$: total halogen, 43.5. Found: total halogen, 43.4.

6-Bromo-2-chlorovanillin.—Vanillin acetate[6] (45 g., 0.232 mole) and anhydrous sodium acetate (45 g.) were added to 225 ml. of glacial acetic acid. Solution was effected by warming the mixture, and then the system was cooled to 45°; 40.5 g. (0.253 mole) of bromine and 0.8 g. of iodine were added. The mixture was stirred for 10 hr. and then poured into 200 ml. of cold water. The oil which separated solidified and the solid was collected by filtration, washed with water, and crystallized from ethanol. 6-Bromovanillin acetate[3] (colorless needles) was obtained; 53.8 g. (0.197 mole, 85% yield); m.p. 116.5–117.5°.

Anal. Calcd. for $C_{10}H_9BrO_4$: Br, 29.27. Found: Br, 29.23.

6-Bromovanillin acetate was nitrated, the acetyl group was removed from the nitration product, and 2-amino-6-bromovanillin was obtained as described by Raiford and Stoesser.[4] A small sample of the intermediate 6-bromo-2-nitrovanillin acetate was purified by crystallization from ethanol, and fine colorless crystals were obtained, m.p. 82.5–83.5°.

Anal. Calcd. for $C_{10}H_8BrNO_6$: Br, 25.16. Found: Br, 25.13.

To 15 ml. of diluted hydrochloric acid (1:1) was added 5 g. (0.0203 mole) of 2-amino-6-bromovanillin; the mixture was stirred to a smooth paste and cooled in an ice bath. Diazotization was accomplished with sodium nitrite (2 g., 0.029 mole), and 3 g. of cuprous chloride in 10 ml. of concd. hydrochloric acid was added. This mixture was cooled in an ice bath for 10 min., allowed to warm to room temperature, heated on a steam bath for 2 hr., and cooled to room temperature. The precipitated solid was collected by filtration, washed with dilute hydrochloric acid, and crystallized from ethanol. 6-Bromo-2-chlorovanillin (pale yellow needles) was obtained; 2.92 g. (0.011 mole, 54% yield); m.p. 148–149°.

Anal. Calcd. for $C_8H_6BrClO_3$: total halogen, 43.5. Found: total halogen, 43.4.

2,5-Dibromo-6-chlorovanillin. A. Bromination of 2-Bromo-6-chlorovanillin.—To a glacial acetic acid solution of 2-bromo-6-chlorovanillin (1 g., 0.0038 mole) and anhydrous sodium acetate (0.4 g.), 0.65 g. (0.0041 mole) of bromine was added, and the mixture was allowed to stand for 24 hr. The precipitate was collected by filtration and washed with glacial acetic acid and with water. Recrystallization of the solid gave 0.393 g. (0.00114 mole, 30% yield), m.p. 175–176°.

B. From 6-Chloro-2-nitrovanillin.—To 6-chloro-2-nitrovanillin[1] (2 g., 0.0086 mole) and 0.8 g. of anhydrous sodium acetate dissolved in warm glacial acetic acid, 1.38 g. (0.0086 mole) of bromine was added; the mixture was allowed to stand for 24 hr. Water was added to precipitate the product; this was collected by filtration and recrystallized from glacial acetic acid. The 5-bromo-6-chloro-2-nitrovanillin was colorless; m.p. 180–181°; yield, 2.46 g. (0.0079 mole, 92%).

Anal. Calcd. for $C_8H_5BrClNO_5$: total halogen, 37.2. Found: total halogen, 37.3.

To a boiling mixture of 10 g. of ferrous sulfate, 15 ml. of concd. ammonia water, and 35 ml. of water, 1 g. (0.0032 mole) of 5-bromo-6-chloro-2-nitrovanillin was added in small portions. Boiling was continued for 15 min., 20 ml. of water was added, and the hot mixture was filtered. The residue was extracted several times with hot ammonia water; the filtrates were combined and cooled. 2-Amino-5-bromo-6-chlorovanillin separated, and it was recrystallized from dilute methanol; m.p 169–170°; yield, 0.539 g. (0.00192 mole, 60%).

2-Amino-5-bromo-6-chlorovanillin was prepared also from 2-amino-6-chlorovanillin[1]; the amino compound (2 g., 0.0099 mole) was dissolved in 35 ml. of glacial acetic acid, and 1.6 g. (0.01 mole) of bromine was added. 2-Amino-5-bromo-6-chlorovanillin precipitated; it was washed with glacial acetic acid and with water and recrystallized from glacial acetic acid; m.p. 169–170°; yield, 2.53 g. (0.009 mole, 90%).

Anal. Calcd. for $C_8H_7BrClNO_3$: total halogen, 41.2. Found: total halogen, 40.9.

A mixture of equal amounts of the two samples of 2-amino-5-bromo-6-chlorovanillin melted without depression of the melting point.

A small sample (0.5 g., 0.00178 mole) of 2-amino-5-bromo-6-chlorovanillin was diazotized; ethanol was added to the mixture, and it was boiled for several minutes. Dilution of the mixture with water, collection of the precipitate by filtration, and recrystallization of the solid product from glacial acetic acid gave 0.143 g. (0.000535 mole, 30% yield) of 5-bromo-6-chlorovanillin, m.p. 211–212°.[1] A mixture of this product and a sample of the compound prepared by the method of Raiford and Lichty[1] melted without depression of the melting point.

To 1 g. (0.00357 mole) of 2-amino-5-bromo-6-chlorovanillin, 3 ml. of 40% hydrobromic acid was added; the mixture was stirred and cooled in an ice bath, and 0.4 g. (0.0058 mole) of sodium nitrite was added. Freshly prepared cuprous bromide (1.5 g.) in 10 ml. of 40% hydrobromic acid was added. The mixture was allowed to warm to room temperature, heated on a steam bath for 1 hr., and cooled. The precipitated solid was collected by filtration, washed with dilute hydrochloric acid and with water, and recrystallized from glacial acetic acid. 2,5-Dibromo-6-chlorovanillin (pale yellow needles) was obtained; 0.713 g. (0.00207 mole, 58% yield); m.p. 176–177°.

Anal. Calcd. for $C_8H_5Br_2ClO_3$: total halogen, 56.7. Found: total halogen, 56.8.

A mixture of samples of this product and that obtained by the bromination of 2-bromo-6-chlorovanillin melted at 175.5–177°.

5,6-Dibromo-2-chlorovanillin.—A small excess of bromine (0.65 g., 0.00406 mole) was added to 1 g. (0.00376 mole) of 6-bromo-2-chlorovanillin and 0.4 g. of anhydrous sodium acetate in glacial acetic acid, and the mixture was allowed to stand for 15 min. Addition of water precipitated a nearly quantitative yield of 5,6-dibromo-2-chlorovanillin, and recrystallization from dilute acetic acid gave pale yellow needles; m.p. 162–163°; 1.11 g. (0.00323 mole, 86% yield).

Anal. Calcd. for $C_8H_5Br_2ClO_3$: total halogen, 56.7. Found: total halogen, 56.7.

(6) R. Pschorr and C. Sumuleanu, *Ber.*, **32**, 3407 (1899).

6-Bromo-2,5-dichlorovanillin. A. From 2-Amino-6-bromovanillin.—2-Amino-6-bromovanillin was prepared by the method of Raiford and Stoesser.[4] This compound (8 g., 0.0325 mole) was dissolved in pyridine, and acetyl chloride (2.6 g., 0.033 mole) was added dropwise with constant stirring. After several minutes, the reaction was complete, and the mixture was poured into an excess of dilute hydrochloric acid. After the solid which separated had been collected by filtration and washed with dilute hydrochloric acid and with water, it was extracted with ether. The solid product obtained after evaporation of the solvent from the ether extract was crystallized from 60% ethanol, and 2-acetamino-6-bromovanillin was obtained in the form of pale lemon-yellow needles; m.p. 107–108°; 7.9 g. (0.0274 mole, 85% yield).

Anal. Calcd. for $C_{10}H_{10}BrNO_4$: Br, 27.77. Found: Br, 27.93.

The acetamino compound (5 g., 0.0174 mole) and 7 g. of anhydrous sodium acetate were dissolved in 35 ml. of glacial acetic acid by warming the mixture to 70°. The mixture was cooled to 40°, and 3 g. (0.042 mole) of chlorine gas was passed through the rapidly stirred mixture at such a rate that the temperature remained below 55°. Stirring was continued for 15 min. after all of the chlorine had been added. When the mixture was allowed to stand in an ice bath, sodium chloride separated; addition of ice water (2 vol.) dissolved the sodium chloride. The dilution and stirring precipitated a yellow-orange product, which was separated by filtration and washed with dilute acetic acid and with water. Recrystallization from ethanol gave 3.4 g. (0.0105 mole, 60% yield) of 2-acetamino-6-bromo-5-chlorovanillin; yellow-orange platelets; m.p. 119–120°.

Anal. Calcd. for $C_{10}H_9BrClNO_4$: total halogen, 35.8. Found: total halogen, 35.6.

A 3-g. quantity (0.00930 mole) of the acetamino compound was hydrolyzed by boiling it for 10 min. in 10% potassium hydroxide solution. The mixture was cooled and neutralized with dilute hydrochloric acid. A yellow precipitate formed and was collected by filtration, washed with water, and crystallized from ethanol. A nearly quantitative yield (2.6 g., 0.00923 mole) of 2-amino-6-bromo-5-chlorovanillin was obtained; brownish yellow platelets; m.p. 179–180°.

Anal. Calcd. for $C_8H_7BrClNO_3$: total halogen, 41.2. Found: total halogen, 40.8.

The preparation of 2-amino-6-bromo-5-chlorovanillin was accomplished also from 6-bromovanillin acetate,[3] which was nitrated as directed by Raiford and Stoesser[4] and gave 6-bromo-2-nitrovanillin. 6-Bromo-2-nitrovanillin (10 g., 0.0362 mole) and *ca.* 0.2 g. of halogen carrier (1 part iodine: 10 parts ferric chloride[5]) were added to 30 ml. of glacial acetic acid, and the mixture was warmed to 75°. Chlorine gas (5.5 g., 0.077 mole) was bubbled through the rapidly stirred mixture (*ca.* 30 min.). Cooling the mixture in an ice bath precipitated 6-bromo-5-chloro-2-nitrovanillin. This was collected by filtration and crystallized from glacial acetic acid; 7.1 g. (0.0229 mole, 64% yield); colorless needles, m.p. 194–195.5°.

Anal. Calcd. for $C_8H_5BrClNO_5$: total halogen, 37.2. Found: total halogen, 36.9.

A 2-g. sample (0.00644 mole) of 6-bromo-5-chloro-2-nitrovanillin was added in small portions to a boiling mixture of 20 g. of ferrous sulfate in 50 ml. of water and 30 ml. of concd. ammonia water. After boiling this mixture for 15 min., additional boiling ammonia water (10 ml. of concd. ammonia water and 20 ml. of water) was added, and the hot mixture was filtered; the residue was washed with more hot, dilute ammonia water; and the filtrates were combined and cooled. Dilute hydrochloric acid was added until the amine precipitated. After crystallization of the solid product from 65% ethanol, 2-amino-6-bromo-5-chlorovanillin was obtained as brownish yellow crystals; 0.9 g. (0.00321 mole, 50% yield); m.p. 179–180°.

A mixture of samples of the compound prepared by the two procedures melted without depression of the melting point.

To prove the structure of 2-amino-6-bromo-5-chlorovanillin, a 0.5-g. sample (0.00178 mole) was diazotized, and the mixture was boiled with ethanol for several minutes. Cooling and dilution with water gave a solid product; several crystallizations from 65% ethanol gave nearly colorless 6-bromo-5-chlorovanillin (needles); 0.2 g. (0.000753 mole, 42% yield); m.p. 198–199.5°.

The melting point of a mixture of this product and 6-bromo-5-chlorovanillin, prepared by the method of Raiford and Lichty,[1] was 198–200°.

2-Amino-6-bromo-5-chlorovanillin (1 g., 0.00357 mole) was dissolved in 7 ml. of 25% hydrochloric acid; the solution was cooled to 0°, and 0 4 g. (0.0058 mole) of sodium nitrite was added in small portions. To the diazonium solution, 0.8 g. of freshly prepared cuprous chloride in 5 ml. of dilute hydrochloric acid was added, and the mixture was warmed slowly and then heated for 1 hr. on a steam bath. The reaction mixture was cooled, and the product which precipitated was washed with dilute hydrochloric acid, dried, and crystallized from methanol. 6-Bromo-2,5-dichlorovanillin was obtained as fine yellow needles; 0.54 g. (0.0018 mole, 50% yield); m.p. 151–162°. Repeated crystallizations from 40% methanol gave pale yellow needles, m.p. 170.5–171.5°.

Anal. Calcd. for $C_8H_5BrCl_2O_3$: total halogen, 50.3. Found: total halogen, 50.0.

B. From 6-Bromo-2-chlorovanillin—A 1-g. sample (0.00377 mole) of 6-bromo-2-chlorovanillin was dissolved in 15 ml. of warm glacial acetic acid, and *ca.* 0.1 g. of iodine–ferric chloride mixture (1:10) was added. While it was warmed at 80°, 0.6 g. (0.00845 mole) of chlorine was bubbled through the reaction mixture, and then stirring was continued for 20 min. Ice water (2 vol.) was added, and the yellow solid which separated was washed several times with dilute ethanol. Crystallization from dilute ethanol gave 0.6 g. (0.002 mole, 53% yield) of nearly colorless 6-bromo-2,5-dichlorovanillin, m.p. 170–171°.

A mixture of samples of this product and that prepared by the Sandmeyer reaction melted at 170–171.5°.

2,6-Dibromo-5-chlorovanillin. A. From 2-Amino-6-bromo-5-chlorovanillin.—A 0.5-g. sample (0.00178 mole) of 2-amino-6-bromo-5-chlorovanillin was dissolved in 7 ml. of 70% sulfuric acid, and after cooling the solution to 0°, 0.3 g. (0.0043 mole) of sodium nitrite was added. In turn, 0.6 g. of freshly prepared cuprous bromide in 5 ml. of 40% hydrobromic acid was introduced. The mixture was allowed to warm slowly to room temperature and then heated on a water bath for 1.5 hr. Cooling caused a precipitate to separate; crude product, 0.35 g. (0.00102 mole, 57% yield). The crude product was extracted several times with hot *n*-heptane, the extracts were combined, and when the solution was cooled, pale yellow needles separated, m.p. 156–157°.

Anal. Calcd. for $C_8H_5Br_2ClO_3$: total halogen, 56.7. Found: total halogen, 56.6.

B. From 2,6-Dibromovanillin.—A 1-g. quantity (0.00323 mole) of 2,6-dibromovanillin[4] was dissolved in 15 ml. of glacial acetic acid, which contained *ca.* 0.1 g. of iodine–ferric chloride mixture (1:10). The reaction mixture was heated to 80° and maintained at that temperature while 0.6 g. (0.00845 mole) of chlorine was bubbled through it. After all of the chlorine had been added, the mixture was allowed to stand for 30 min., cooled to 5°, and diluted with ice water (2 vol.). A precipitate formed; this was collected by filtration and washed with dilute acetic acid and with water. Crystallization from 75% ethanol gave 0.46 g. (0.00133 mole, 41% yield) of 2,6-dibromo-5-chlorovanillin, m.p. 156–157.5°.

No depression of melting point was observed when a mixed melting point determination was carried out with equal amounts of the products prepared by the two procedures.

2-Bromo-5,6-dichlorovanillin. A. From 2-Amino-6-chlorovanillin.—To 5 g. (0.0248 mole) of 2-amino-6-chlorovanillin[1] dissolved in 15 ml. of pyridine, 2 g. (0.0254 mole) of acetyl chloride was added dropwise; the mixture was allowed to stand for 5 min. and then poured into excess dilute hydrochloric acid. The crude acetyl derivative separated, was collected by filtration, and was washed several times with dilute hydrochloric acid and with water. The solid was extracted with ether (to remove the ether-soluble acetamino compound from amine hydrochloride). From the ether solution, 2-acetamino-6-chlorovanillin was recovered, and it was crystallized from 60% ethanol; 4.6 g. (0.0189 mole, 76% yield); m.p. 90–91°.

Anal. Calcd. for $C_{10}H_{10}ClNO_4$: Cl, 14.58. Found: Cl, 14.67.

A 3-g. amount (0.0123 mole) of 2-acetamino-6-chlorovanillin and 3 g. of anhydrous sodium acetate were dissolved in 25 ml. of glacial acetic acid, and chlorine (1.8 g., 0.0253 mole) was bubbled through the solution at such a rate that the temperature did not rise above 55°. After the chlorine had been introduced, the mixture was stirred for 20 min. and then cooled in an ice bath. Water (2 vol.) was added to dissolve the sodium chloride, which had separated. Stirring the diluted mixture caused a yellow precipitate, which was collected by filtration and washed with dilute acetic acid and with water, to separate. 2-Acetamino-5,6-dichlorovanillin was crystallized from ethanol and obtained as yellow platelets; 2.2 g. (0.00784 mole, 64% yield); m.p. 127–128°.

Anal. Calcd. for $C_{10}H_9Cl_2NO_4$: Cl, 25.54. Found: Cl, 25.46.

Hydrolysis of the amide was accomplished in nearly quantitative yield by boiling a small sample in 15% potassium hydroxide solution for 10 min. The reaction mixture was cooled and neutralized with dilute hydrochloric acid, and the precipitated 2-amino-5,6-dichlorovanillin was crystallized from dilute ethanol, m.p. 191.5–192°.[7]

Anal. Calcd. for $C_8H_7Cl_2NO_3$: Cl, 30.08. Found: Cl, 30.09.

2-Amino-5,6-dichlorovanillin was prepared also from 6-chloro-2-nitrovanillin. 6-Chloro-2-nitrovanillin[1] (5 g., 0.0216 mole) and *ca.* 0.1 g. of iodine–ferric chloride mixture (1:10) were added to 20 ml. of glacial acetic acid, and the mixture was warmed to 75°. This was stirred, and during 25 min., chlorine gas (2 g., 0.0282 mole) was passed through the mixture. The reaction mixture was cooled in an ice bath; stirring and dilution with water gave a yellow precipitate. 5,6-Dichloro-2-nitrovanillin was collected by filtration, washed with dilute acetic acid, and crystallized from dilute acetic acid; 4 g. (0.015 mole, 69% yield); m.p. 173–174°.

Anal. Calcd. for $C_8H_5Cl_2NO_5$: Cl, 26.69. Found: Cl, 26.73.

The nitro compound (2 g., 0.00752 mole) was reduced with ferrous sulfate–ammonia water by the procedure described above for the reduction of 5-bromo-6-chloro-2-nitrovanillin, and 2-amino-5,6-dichlorovanillin was obtained in 72% yield (1.3 g., 0.00551 mole); recrystallization from 75% ethanol gave a product which melted at 191.5–193°.

The melting point of a mixture of samples of the compound prepared by the two procedures was 191.5–193°.

2-Amino-5,6-dichlorovanillin (1 g., 0.00423 mole) was dissolved in 5 ml. of 40% hydrobromic acid, the solution was cooled to 0°, and diazotization was effected with 0.4 g. (0.0058 mole) of sodium nitrite. To this 0.7 g. of freshly prepared cuprous bromide in 5 ml. of 40% hydrobromic acid was added. The mixture was allowed to warm to room temperature, heated on a steam bath for 1 hr., and cooled. The precipitated product was collected by filtration, washed with dilute hydrochloric acid and with water, and crystallized from 40% methanol. 2-Bromo-5,6-dichlorovanillin was obtained as fine, colorless platelets; 0.8 g. (0.00267 mole, 63% yield); m.p. 164–165°.

(7) A mixed melting point determination was carried out with 2-amino-6-chlorovanillin[1] (m.p. 194–195°); the mixture melted over the range: 170–185°.

Anal. Calcd. for $C_8H_5BrCl_2O_3$: total halogen, 50.3. Found: total halogen, 50.2.

B. From 2-Bromo-6-chlorovanillin.—A 1-g. amount (0.00376 mole) of 2-bromo-6-chlorovanillin and *ca.* 0.1 g. of iodine–ferric chloride mixture (1:10) were added to 15 ml. of glacial acetic acid, and the mixture was warmed to 80°. While this temperature was maintained, chlorine gas (0.6 g., 0.00845 mole) was passed into the reaction mixture; then it was allowed to stand for 3 hr. Addition of ice water (2 vol.) and stirring precipitated a solid which was collected by filtration, washed with dilute acetic acid and with water, and crystallized from 75% ethanol; 0.4 g. (0.00133 mole, 35% yield) of 2-bromo-5,6-dichlorovanillin was obtained, m.p. 164–165°.

No depression of the melting point was observed when a mixed melting point determination was carried out with samples of the compound prepared by the two different methods.

Bromination of 6-Bromo-2-nitrovanillin.—A 1-g. quantity (0.00362 mole) of 6-bromo-2-nitrovanillin was dissolved in 10 ml. of warm glacial acetic acid, and 0.8 g. (0.005 mole) of bromine was added. The red color disappeared promptly. The solution was cooled in an ice bath, and a nearly quantitative yield (1.25 g., 0.00352 mole, 97%) of 5,6-dibromo-2-nitrovanillin was precipitated. This was crystallized from glacial acetic acid and melted at 195–196.5°.

Anal. Calcd. for $C_8H_5Br_2NO_5$: Br, 45.07. Found: Br, 45.29.

Chlorination of 6-Chlorovanillin.—Attempts were made to chlorinate 6-chlorovanillin with chlorine: a) in chloroform solution with iodine as catalyst at 60°; b) in glacial acetic acid solution with iodine as catalyst at 80°; c) in pyridine solution with iodine as catalyst at 60°. In each case, only starting material was recovered.

6-Chlorovanillin[1] (2 g., 0.0107 mole) was dissolved in 25 ml. of glacial acetic acid (heated to 100°), and *ca.* 0.1 g. of iodine–ferric chloride mixture (1:10) was added. The mixture was maintained at 80° while 0.8 g. (0.0113 mole) of chlorine was bubbled through it; a solid precipitated. Then the mixture was allowed to stand for 30 min.; finally it was cooled in ice water. The solid product was collected by filtration and crystallized from ethanol; 1.8 g. (0.00814 mole, 76% yield) of 5,6-dichlorovanillin, m.p. 189–190°, was obtained.

5,6-Dichlorovanillin was prepared also from vanillin triacetate by the method of Raiford and Lichty,[1] m.p. 189.5–191°.

A mixture of samples prepared by the two procedures melted at 189.5–190.5°.

Bromination of 6-Bromovanillin.—6-Bromovanillin[8] (2 g., 0.00866 mole) was dissolved in 20 ml. of glacial acetic acid, and a trace of iodine was added. The addition of 1.3 g. (0.00813 mole) of bromine readily gave 2.1 g. (0.00677 mole, 83% yield) of 5,6-dibromovanillin,[8] m.p. 213–214° (from glacial acetic acid).

Chlorination of 2-Nitrovanillin.—Attempts were made to chlorinate 2-nitrovanillin with chlorine: a) in glacial acetic acid solution with ferric chloride and with iodine as catalysts at 50, 70, and 90°; b) in methanol solution with ferric chloride and with iodine as catalysts at 60°; c) in pyridine solution with iodine as catalyst at 60°. An attempt was made also to chlorinate 2-nitrovanillin with sulfuryl chloride in chloroform solution at 50°. In each case, only starting material was recovered.

A 5-g. quantity (0.0254 mole) of 2-nitrovanillin[4] and *ca.* 0.1 g. of iodine were dissolved in 50 ml. of chloroform. While the solution was refluxed gently (30 min.), 2 g. (0.0282 mole) of chlorine gas was passed through it. The reaction mixture was allowed to stand overnight at room temperature. Evaporation of part of the solvent resulted

(8) L. C. Raiford and G. C. Hilman, *J. Am. Chem. Soc.*, **49**, 1575 (1927).

in the separation of a solid which was collected by filtration and crystallized from 75% ethanol; 4.6 g. (0.0198 mole, 78% yield); m.p. 134.5–136°.

A mixture of equal parts of this product and starting material melted between 120 and 127°; a mixture of the product and 5-chloro-2-nitrovanillin, prepared by the method of Raiford and Lichty,[1] melted without depression at 134.5–136°.

Chlorination of 5-Chlorovanillin Triacetate.—5-Chlorovanillin triacetate was chlorinated by the method of Raiford and Lichty[1]; a 78% yield of 5,6-dichlorovanillin triacetate; m.p. 114–115°, was obtained.

Attempted Bromination of 5-Chlorovanillin Triacetate.—5-Chlorovanillin triacetate (10 g., 0.0303 mole) was dissolved in 50 ml. of glacial acetic acid by warming the mixture to 60°; 8.4 g. (0.0525 mole) of bromine was added, and the solution was refluxed for 2 hr. After cooling the reaction mixture, it was poured into 3 vol. of water. The precipitate which formed was crystallized from 30% ethanol; 8.2 g.; m.p. 114–115°. By a mixed melting point determination (m.p. 114–115°) with starting material, the product was identified as 5-chlorovanillin triacetate. The 8.2 g. of material represented an 82% (0.0248 mole) recovery of starting material.

Structures Related to Morphine. XXIII.[1] Stereochemistry of 5,9-Dialkyl-6,7-benzomorphans

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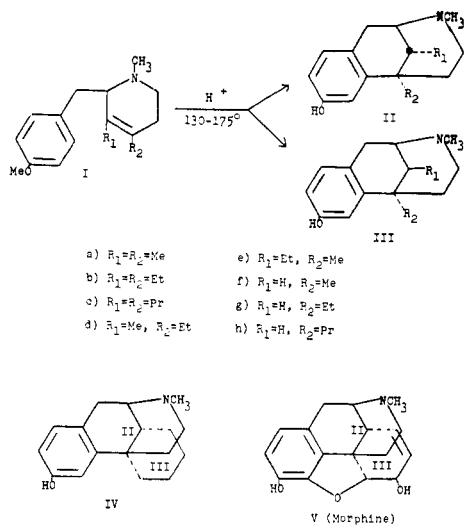
The absolute configuration (at C-9) of several 5,9-dialkyl-6,7-benzomorphans (II, III) has been adduced from methiodide-rate-formation and NMR studies. A nonaqueous titration procedure for determining unchanged II and III, and thus the amount of methiodide formed in a given time, is described.

The acid-catalyzed cyclization of 3,4-dialkyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridines (I) leads to isomeric 5,9-dialkyl-6,7-benzomorphans (II, III) differing in configuration at position 9.[3–6] It has been presumed that the *predominant* isomers[7] resulting from these cyclizations[8] are those in which the 9-alkyl substituents (R_1) are oriented away from the nitrogen, *i.e.*, axial for the hydroaromatic ring, as in II. This assumption followed from analogy with the morphinan synthesis[9] and from consistency with the "*trans* rule" of addition to olefinic bonds,[10] in this instance to the 3,4-double bond of I. In view of the significant pharmacologic behavior of these compounds, particularly the β-isomers,[3,4] it was desired to determine unequivocally their stereochemistry at C-9.



From an examination of molecular models of II and III,[11] it appeared that there would be a substantial difference in the rate of formation of their methiodides, and during the course of degradative experiments in the dimethyl series (IIa and IIIa) such a rate difference was casually observed. It seemed likely also that the methyl signal in the NMR spectrum of IIa would be distinguishable from that of IIIa. These predictions have proved valid and we wish to report a quantitative estimation of the rate of formation of the methiodides of IIa–e and IIIa–e along with NMR spectra of IIa, IIIa, and their *O*-acetyl derivatives. Included as controls in the rate studies are IIf–h

(1) Paper XXII, H. Kugita, S. Saito, and E. L. May, *J. Med. Pharm. Chem.*, **5**, 357 (1962).

(2) Visiting Fellow from the Chelsea School of Pharmacy, England; present address: London, England.

(3) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(4) J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962).

(5) S. E. Fullerton and E. L. May, paper in preparation.

(6) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Org. Chem.*, to be published.

(7) For convenience and clarity the predominant isomers will be designated with the prefix α; the lesser diastereomers will be designated β.

(8) The ratio of predominant (α) to lesser (β) isomers has varied from 12:1 to 6:1 and appears to depend upon the cyclizing agent and temperature used as well as the bulk of the R groups. In general, the higher the temperature and the larger the alkyl groups the lower is this ratio. The yields of the lesser (β) isomers are usually 3–8%.

(9) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(10) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, New York; Chapman Hall, Ltd., London, 1956, p. 242.

(11) The nitrogen of III is crowded by R_1 while in II there is, of course, no discernible hindrance of the nitrogen by R_1.