[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Synthesis of an Analog of Chloramphenicol[1]

BY WILLIAM T. CALDWELL AND GEORGE C. SCHWEIKER

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A method for the synthesis of the antibiotic, chloramphenicol, has been modified and extended to the preparation of a compound containing a trifluoromethyl group, instead of a nitro group, in the para position of the phenyl ring. An epimerization encountered during one of the alternate preparations of this compound, *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX), relates it, and several others prepared here, to pseudoephedrine by analogy. *In vivo* tests indicate that IX exhibits antibacterial activity against *Klebsiella pneumoniae* and has a low toxicity in mice.

The nitro group of chloramphenicol has been replaced by methyl and methoxy groups by Buu-Hoi, Xuong and Khoi[2]; by methoxy and phenoxy groups by Rebstock and Pfeiffer[3]; by fluorine, chlorine, bromine and iodine by Bambas, Troutman and Long[4]; and by alkylmercapto and arylmercapto groups by Cutler, Stenger and Suter.[5] In this work, the electronegative trifluoromethyl group was substituted for the nitro group of chloramphenicol in order to see if electronegativity or reducibility of the nitro group was a critical factor in biological activity.

To synthesize this compound, *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX), the method used by Long and Troutman[6] for the synthesis of chloramphenicol was followed in general. The procedure of Bowman[7] was used in preparing *p*-trifluoromethylacetophenone (I) from *p*-trifluoromethylbenzoyl chloride made from 1,4-bis-(trifluoromethyl)-benzene obtained from the Hooker Electrochemical Company. The substituted acetophenone I was brominated in the α-position under conditions similar to those used by Long and Troutman[8] for the bromination of 4-nitro-1-acetonaphthone. However, numerous attempts to prepare the hexamethylenetetramine salt of *p*-trifluoromethyl-α-bromoacetophenone (II) failed in our hands. A modification of the Long and Troutman[6] synthesis of chloramphenicol and related compounds was therefore necessary for the preparation of the *p*-trifluoromethyl analog IX. Accordingly, II was treated with potassium phthalimide in dimethyl formamide as solvent[9] to give *p*-trifluoromethyl-α-phthalimidoacetophenone (III), which was partially hydrolyzed with alcoholic potassium hydroxide[10,11] into *p*-trifluoromethyl-α-(*o*-carboxybenzamido)-acetophenone (IV). Acid hydrolysis[10,11] of IV gave *p*-trifluoromethyl-α-aminoacetophenone hydrochloride (V).

From this stage of the synthesis, two routes for the preparation of IX were followed. In one method, V was dichloroacetylated by treatment with dichloroacetyl chloride in boiling toluene.[5] The resulting *p*-trifluoromethyl-α-dichloroacetamidoacetophenone (VI) was methylolated in ethanol with formaldehyde and sodium bicarbonate as catalyst to give *p*-trifluoromethyl-α-dichloroacetamido-β-hydroxypropiophenone (VII), a reaction similar to one of the methylolation reactions used by Cutler, Stenger and Suter.[5] A dimethylolated by-product, *p*-trifluoromethyl-α-dichloroacetamido-β,β'-dihydroxyisobutyrophenone (VIII) was also formed during this reaction, but only in significant amounts if the reaction time was lengthened beyond seven hours. A Meerwein–Ponndorf–Verley reduction of VII without continuous removal of acetone[12,5] gave *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX) and *erythro*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (X) in a ratio of approximately 15 of *threo* to 1 of *erythro*.

In the alternate route for the preparation of IX, the amine salt V was acetylated with acetic anhydride and sodium acetate[6] to give *p*-trifluoromethyl-α-acetamidoacetophenone (XI), which was methylolated with formaldehyde and a mixture of sodium bicarbonate and sodium carbonate, in a manner similar to that used by Long and Jenesel[13] to make *o*-nitro-α-acetamido-β-hydroxypropiophenone. The resulting *p*-trifluoromethyl-α-acetamido-β-hydroxypropiophenone (XII) was reduced in a manner similar to the reduction of VII, but in this anomalous case, almost equal amounts of *threo*-2-acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (XIII) and *erythro*-2-acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (XIV) were isolated from the reaction mixture. A further anomaly in this case is that the melting point of the *threo*-N-acetyl intermediate XIII is higher than that of its diastereoisomer XIV.

Hot 5% hydrochloric acid was used to hydrolyze the N-acetyl intermediates (XIII and XIV) and the *threo*-N-dichloroacetyl compound IX in a way similar to that used by Bambas, Troutman and Long[4] for the preparations of the 2-amino-1-*p*-halogenphenyl-1,3-propanediols. In all three cases, only the *threo*-2-amino-1-*p*-trifluoromethylphenyl-1,3-propanediol (XI) was recovered. It was noticed during the hydrolysis of the N-acetyl intermediates (XIII and XIV) that solution of the *threo* compound XIII in the reaction mixture occurred much more quickly than did solution of the *erythro* compound XIV in similar media. Also, crystallization of the *threo*-amine XV in good yield occurred almost at once from the reaction mixture of XIII,

(1) Taken from a dissertation submitted by George C. Schweiker to the Temple University Graduate Council in partial fulfillment of the requirements for the Ph.D. degree.

(2) MM. Buu-Hoi, D. Xuong and H. Khoi, *J. Chem. Soc.*, 255 (1951).

(3) M. Rebstock and E. Pfeiffer, THIS JOURNAL, **74**, 3207 (1952).

(4) L. Bambas, H. Troutman and L. Long, *ibid.*, **72**, 4445 (1950).

(5) R. Cutler, R. Stenger and C. Suter, *ibid.*, **74**, 5475 (1952).

(6) L. Long and H. Troutman, *ibid.*, **71**, 2473 (1949).

(7) R. Bowman, *J. Chem. Soc.*, 322 (1950).

(8) L. Long and H. Troutman, THIS JOURNAL, **73**, 542 (1951).

(9) J. Sheehan and W. Bolhofer, *ibid.*, **72**, 2786 (1950).

(10) C. Goedeckemeyer, *Ber.*, **21**, 2686 (1888).

(11) S. Gabriel, *ibid.*, **41**, 1132 (1908).

(12) W. Truett and W. Moulton, THIS JOURNAL, **73**, 5913 (1951).

(13) L. Long and N. Jenesel, *ibid.*, **72**, 4299 (1950).

while crystallization of the *threo*-amine XV was very slow from the reaction mixture of XIV and was recovered in lower yield.

The amine XV obtained by hydrolysis of either XIII, XIV or IX was treated with ethyl dichloroacetate, in a manner similar to that used by Cutler, Stenger and Suter[5] for the preparation of the *p*-methylmercapto analog of chloramphenicol, to form a N-dichloroacetyl compound which was identical with the compound IX prepared by the alternate method of synthesis. Treatment of the same amine XV with acetic anhydride, followed by a Kunz[14] hydrolysis to ensure that no esterified substance be present, a process similar to one of the acylation procedures described by Rebstock,[15] produced a compound identical with XIII. Since inversion during acylation does not occur with analogous compounds, this reaction confirms that epimerization occurred during the hydrolysis of XIV.

Although epimerization of the *erythro* diastereoisomers of chloramphenicol and its analogs with hot 5% hydrochloric acid apparently has not previously been encountered, epimerization of these *erythro*-N-acylated compounds into their corresponding *threo*-amines during treatment with thionyl chloride and hydrolysis has been reported by Moersch and Moore.[16] An analogous case has also been reported by Bergmann[17] in the epimerization of the N-formyl derivative of *erythro*-α,β-diphenyl-β-hydroxyethylamine into *threo*-α,β-diphenyl-β-hydroxyethylamine. Perhaps the closest analogy to the inversion reaction which took place here is in the reactions studied by Welsh,[18] in which hot 5% hydrochloric acid converted N-acetylephedrine (*erythro* configuration) and other N-substituted ephedrines into pseudoephedrine (*threo* configuration). In all of these analogous cases, the *threo*-N-derivatives showed no or practically no epimerization into the corresponding *erythro* compounds when treated in a similar fashion.

Since the configurations of the ephedra series have been determined,[19-23] the epimerization encountered in this work indicates, by analogy, that compound XV is *threo*-2-amino-1-*p*-trifluoromethylphenyl-1,3-propanediol. Compounds IX and XIII, which were made from XV by reactions which did not cause inversions, must therefore be *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol and *threo*-2-acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol, respectively; their corresponding diastereoisomers, compounds X and XIV must be *erythro*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol and *erythro*-2-acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol, respectively.

Tests by The Lilly Research Laboratories indicate that *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX) is active, but mg. for mg. less effective than sulfanilamide in *Streptococcus pyogenes* infected mice and also in typhoid infected mice, each at 5 mg. orally × 2; it is effective in *Klebsiella pneumoniae* infected mice at 5 mg. orally × 2.

We wish to thank the Hooker Electrochemical Company for directions[24] for the preparation of *p*-trifluoromethylbenzoic acid and for a gift of chemicals, Eli Lilly and Company for carrying out pharmacological tests,[25] and the Temple University Committee on Research and Publications for a Grant-in-aid.

Experimental[26]

***p*-Trifluoromethyl-α-bromoacetophenone** (II).—Conditions similar to those used by Long and Troutman[8] for the bromination of 4-nitro-1-acetonaphthone were used in the preparation of II.

Equimolar solutions of bromine and *p*-trifluoromethylacetophenone (I), b.p. 81–84° at 8–9 mm., in glacial acetic acid containing a catalytic amount of concd. hydrochloric acid gave white crystalline II after dilution with ice-water. The product was dissolved in ether and dried over anhydrous magnesium sulfate. Evaporation of the ether *in vacuo* gave 96% yields of II, m.p. 47–50°. An analytical sample was recrystallized from carbon tetrachloride, m.p. 54–55°.

Anal. Calcd. for $C_9H_6BrF_3O$: Br, 29.93. Found: Br, 30.31.

Hexamethylenetetramine hydrobromide resulted from numerous attempts to make the urotropine salt of II. Variations in temperature, reaction time and concentrations of reactants in three different solvents (chlorobenzene,[6] chloroform[27] and acetonitrile[6]) gave the same decomposition product, m.p. 192–193° dec.

Anal. Calcd. for $C_6H_{13}BrN_4$: N, 25.34. Found: N, 24.88.

***p*-Trifluoromethyl-α-phthalimidoacetophenone** (III) was prepared by using conditions similar to those used by Sheehan and Bolhofer[9] for the preparation of α-phthalimidoacetophenone.

A suspension of 229 g. (1.24 moles) of potassium phthalimide in 1200 ml. of dimethyl formamide was stirred while 315 g. (1.18 moles) of II was added. After an exothermic reaction had subsided, the blood-red mixture was heated on the steam-bath for 1 hour. (Longer or stronger heating decreases the yield considerably.) After cooling, 1800 ml. of chloroform was added and the mixture was poured into 6 l. of water. The aqueous phase was separated and washed with three portions of chloroform and the chloroform was washed with 1 l. of cold 2% sodium hydroxide solution followed by 1 l. of water. After drying over anhydrous magnesium sulfate, the chloroform was distilled to a small volume and cooled. The resulting precipitate was triturated with 500 ml. of cold ether, collected on a filter, and washed with cold ether. The white crystalline product III weighed 265 g. (67.5%), m.p. 181–182°. An analytical sample was recrystallized from chloroform–absolute ethanol, m.p. 181–182°.

Anal. Calcd. for $C_{17}H_{10}F_3NO_3$: C, 61.26; H, 3.00; N, 4.20. Found: C, 61.47; H, 3.22; N, 4.14.

***p*-Trifluoromethyl-α-(*o*-carboxybenzamido)-acetophenone** (IV) was made by partial hydrolysis of III under conditions similar to those used by Goedeckemeyer,[10] and by Gabriel,[11] for the partial hydrolysis of α-phthalimidoacetophenone.

Two hundred and sixty-five grams (0.796 mole) of III was added with stirring to 500 ml. of a hot alcoholic solution of 52 g. of 87% (0.805 mole) potassium hydroxide, and stirring was continued for 30 minutes after addition was

(14) A. Kunz and C. Hudson, THIS JOURNAL, **48**, 1982 (1926).
(15) M. Rebstock, *ibid.*, **72**, 4800 (1950).
(16) G. Moersch and A. Moore, U. S. Patent 2,513,346 (1950).
(17) E. Bergmann, THIS JOURNAL, **73**, 1216 (1951).
(18) L. Welsh, *ibid.*, **71**, 3500 (1949).
(19) K. Freudenberg, *ibid.*, **54**, 234 (1932).
(20) K. Freudenberg and F. Nikolai, *Ann.*, **510**, 223 (1934).
(21) K. Freudenberg, J. Todd and R. Seidler, *ibid.*, **501**, 199 (1933).
(22) K. Freudenberg and F. Rhino, *Ber.*, **57**, 1547 (1914).
(23) K. Freudenberg, *ibid.*, **47**, 2027 (1914).
(24) Private communication from C. Gochenour, Sales Development, Hooker Electrochemical Company, Niagara Falls, New York.
(25) Private communication from E. Rohrmann, The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.
(26) Melting points are uncorrected. Analyses were performed by the Clark Microanalytical laboratory, Urbana, Illinois.
(27) C. Mannich and F. Hahn, *Ber.*, **44**, 1542 (1911).

complete. The orange solution was diluted with 6 l. of cold water and made strongly acidic with hydrochloric acid. The white crystalline product IV was filtered off, washed well with cold water and dried; yield 269 g. (96%), m.p. 189–192°. An analytical sample was recrystallized twice from glacial acetic acid, m.p. 196–198°.

Anal. Calcd. for $C_{17}H_{12}F_3NO_4$: C, 58.12; H, 3.44. Found: C, 58.33; H, 3.26.

***p*-Trifluoromethyl-α-aminoacetophenone Hydrochloride (V).**—Hydrolysis of IV was effected by hot hydrochloric acid solution in a fashion similar to that used by Goedeckemeyer,[10] and by Gabriel,[11] for the hydrolysis of α-(*o*-carboxybenzamido) - acetophenone. However, a modified method of isolation had to be used to get a good yield of V.

A mixture of 269 g. (0.77 mole) of IV and 600 ml. of concd. hydrochloric acid in 600 ml. of water was refluxed for 2 hours, and then evaporated to dryness. The residue was stirred with 400 ml. of boiling absolute ethanol, cooled to room temperature, and filtered. The product was washed with 100 ml. of absolute ethanol and then with ether until white. The hydrochloride salt V weighed 165 g. (90%), m.p. 248–250° dec. An analytical sample was recrystallized from absolute ethanol containing a few drops of dilute hydrochloric acid, m.p. 251–252° dec.

Anal. Calcd. for $C_9H_9ClF_3NO$: N, 5.85. Found: N, 6.03.

***p*-Trifluoromethyl-α-dichloroacetamidoacetophenone (VI).**—Cutler, Stenger and Suter[5] indicated that toluene was a good solvent for the dichloroacetylation of the *p*-methylmercapto derivative of α-aminoacetophenone hydrochloride.

Accordingly, a mixture of 12 g. (0.05 mole) of V and 8.1 g. (0.055 mole) of dichloroacetyl chloride in 125 ml. of toluene was boiled under reflux for 90 minutes. The resulting solution was stirred with charcoal and filtered hot, and the filtrate was cooled and diluted with 250 ml. of ligroin. The white crystalline product was filtered off and washed with ligroin. A yield of 13.5 g. (85.5%) of crude VI was obtained, m.p. 133–137°. (The pure product may be obtained in slightly smaller yield by not diluting the toluene solution with ligroin.) An analytical sample recrystallized from benzene melted at 142–143°.

Anal. Calcd. for $C_{11}H_8Cl_2F_3NO_2$: Cl, 22.58. Found: Cl, 22.20.

***p*-Trifluoromethyl-α-dichloroacetamido-β-hydroxypropiophenone (VII)** was made by a methylolation similar to one of the methylolation reactions described by Cutler, Stenger and Suter.[5]

A mixture of 10.7 g. (0.034 mole) of VI in 25 ml. of 95% ethanol, to which had been added a mixture of 0.5 g. of sodium bicarbonate in 5 ml. of 37% (0.062 mole) aqueous formaldehyde, was stirred and warmed at 40–45° for 7 hours. The suspended sodium bicarbonate was filtered from the warm reaction mixture, and the filtrate was diluted to 150 ml. with water. The resulting precipitate was cooled, filtered off and washed thoroughly with cold water. Two recrystallizations from benzene gave 6.2 g. (53%) of white crystalline VII, m.p. 115–117°. An analytical sample was recrystallized from ether and then benzene, m.p. 117–118°.

Anal. Calcd. for $C_{12}H_{10}Cl_2F_3NO_3$: N, 4.07. Found: N, 4.01.

***p*-Trifluoromethyl-α-dichloroacetamido-β,β'-dihydroxyisobutyrophenone (VIII).**—When a reaction similar to the one described above was carried out with 9 hours of heating rather than 7 hours, the yield of VII was decreased to 48% and 1 g. of benzene insoluble by product VIII was isolated, m.p. 168–170°. An analytical sample was recrystallized from methanol–water, m.p. 169–170°.

Anal. Calcd. for $C_{18}H_{12}Cl_2F_3NO_4$: C, 41.73; H, 3.23. Found: C, 41.87; H, 3.55.

***threo*-2-Dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX).**—A modification of the Meerwein–Ponndorf–Verley reduction described by Truett and Moulton[12] and used by Cutler, Stenger and Suter[5] was used for the reduction of VIII.

To a hot mixture of 30 g. (0.148 mole) of aluminum isopropoxide in 350 ml. of dry isopropyl alcohol was added 25.5 g. (0.0742 mole) of VIII. After refluxing for two hours on the steam-bath, the alcohol was removed by vacuum distillation. The residue was heated on the steam-bath for 30 minutes with 50 ml. of 10% sodium chloride solution and filtered. The filter cake of aluminum hydroxide was washed thoroughly with ether, and the aqueous filtrate was extracted with ether. The combined red ethereal solution was dried over Drierite and filtered with charcoal. Distillation of the solvent left a red residue which was crystallized from 40 ml. of ethylene chloride. The crude product IX was collected on a filter and washed with cold ethylene chloride. Recrystallization from ethylene chloride and washing with cold chloroform gave 11 g. (43%) of white crystalline IX, m.p. 137.5–138.5°. Samples for analysis and antibiotic tests were recrystallized from ethylene chloride, m.p. 137.5–138.5°.

Anal. Calcd. for $C_{12}H_{12}Cl_2F_3NO_3$: C, 41.64; H, 3.49. Found: C, 41.49; H, 3.60.

***erythro*-2-Dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (X)** was isolated from the reaction mixture of the above described experiment by allowing the original ethylene chloride filtrate from the crystallization of the reaction product to stand for 24 hours. The new white crystalline substance which formed was filtered off and washed with chloroform. The yield of X was 0.7 g. (2.7%), m.p. 169–172°. An analytical sample was recrystallized from ethylene chloride, m.p. 174–175°.

Anal. Calcd. for $C_{12}H_{12}Cl_2F_3NO_3$: Cl, 20.49. Found: Cl, 20.06.

***p*-Trifluoromethyl-α-acetamidoacetophenone (XI).**—A method similar to that described by Long and Troutman[6] for the synthesis of the corresponding chloramphenicol intermediate was used to acetylate *p*-trifluoromethyl-α-aminoacetophenone (V).

Two grams (0.0083 mole) of V was acetylated in ice-water with 2.4 g. of acetic anhydride and a solution of sodium acetate trihydrate in 12 ml. of water. Yield of crude product, 2 g., m.p. 152–156°. Recrystallization from benzene gave 1.7 g. (83%) of white crystalline XI, m.p. 162–164°. An analytical sample was recrystallized from ethyl acetate, m.p. 164–165°.

Anal. Calcd. for $C_{11}H_{10}F_3NO_2$: N, 5.71. Found: N, 5.39.

***p*-Trifluoromethyl-α-acetamido-β-hydroxypropiophenone (XII)** was made by a method similar to that used by Long and Jenesel[13] to prepare *o*-nitro-α-acetamido-β-hydroxypropiophenone.

To a stirred mixture of 24.5 g. (0.1 mole) of XI in 8 ml. of methanol and 9.5 ml. of 37% (0.12 mole) of aqueous formaldehyde at 35° was added a solution of 0.93 g. of sodium bicarbonate and 0.31 g. of sodium carbonate in 16 ml. of water. After 25 minutes most of the starting material had dissolved and within another 15 minutes a white solid began to precipitate. The mixture was stirred for another hour at 35°, cooled in ice, and filtered. The crude product was washed thoroughly with water, dried and recrystallized from benzene. Twenty-two grams (80%) of white crystalline XII was collected, m.p. 123–124°. An analytical sample was recrystallized from benzene, m.p. 123–124°.

Anal. Calcd. for $C_{12}H_{12}F_3NO_3$: N, 5.09. Found: N, 5.03.

***threo*-2-Acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (XIII)** was made by essentially the same procedure as that described for the preparation of *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX). Because of the insolubility of XIII in ether, however, ethylene chloride and ethyl acetate were used to extract the filter cake of aluminum hydroxide and the aqueous filtrate. Removal of these solvents left an oil which was dissolved in hot ethylene chloride and cooled. After standing several hours, a white crystalline precipitate formed which was filtered off and washed with ethylene chloride. This was a mixture of diastereoisomers (27% yield together) which melted at 160–164°. Extraction of the mixture with hot ethyl acetate left the *threo*-product XIII as residue which was recrystallized from methanol to give 1.6 g. of white crystalline XIII, m.p. 193–194°. An analytical sample was recrystallized from methanol, m.p. 194–195°.

Anal. Calcd. for $C_{12}H_{14}F_3NO_3$: C, 51.98; H, 5.09. Found: C, 52.19; H, 5.14.

***erythro*-2-Acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (XIV)** was isolated from the reaction mixture of

the above described experiment by reducing in volume and cooling the hot ethyl acetate filtrate obtained from the extraction of the mixture of diastereoisomers. The white crystalline product XIV which formed was filtered off and washed with cold ethyl acetate. The yield of XIV was 1.4 g., m.p. 173–174°. An analytical sample was recrystallized from ethyl acetate, m.p. 173–174°.

Anal. Calcd. for $C_{12}H_{14}F_3NO_3$: C, 51.98; H, 5.09. Found: C, 52.38; H, 5.24.

threo-2-Amino-1-*p*-trifluoromethylphenyl-1,3-propanediol (XV) was formed by the hydrolysis of three compounds, the *threo*-N-dichloroacetyl compound IX, and the *threo*- and *erythro*-N-acetyl intermediates (XIII and XIV), under conditions similar to those used by Bambas, Troutman and Long[4] for the preparation of the 2-amino-1-*p*-halogenphenyl-1,3-propanediols.

Each of the above three substances was hydrolyzed separately with hot 5% hydrochloric acid to give the same white crystalline product XV, m.p. 123–124° after recrystallization from water. Mixed melting points of any two, as well as of all three, were undepressed.

Anal. Calcd. for $C_{10}H_{12}F_3NO_2$: N, 5.96. Found: N, 5.98.

Dichloroacetylation of XV was effected by treatment with ethyl dichloroacetate in a manner similar to that used by Cutler, Stenger and Suter[5] for the preparation of the *p*-methylmercapto analog of chloramphenicol.

The N-dichloroacetyl derivatives so obtained were identical, m.p. 137.5–138.5°. Mixed melting points of them as well as with the *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX) prepared by the alternate method of synthesis were undepressed.

Acetylation of XV with acetic anhydride followed by selective hydrolysis[14] of any acyloxy groups, was carried out in a manner similar to one of the acylation procedures described by Rebstock[15] for the acylation of the free base of chloramphenicol.

The *threo*-2-acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (XIII) so formed melted at 194–195° after recrystallization from methanol.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

A Dimethoxy Substituted Harman and Other Compounds Derived from 5,6-Dimethoxyindole

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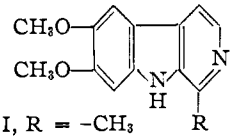
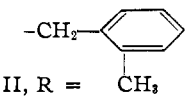
A practical method for the synthesis of 5,6-dimethoxyindole involving the hydrogenation of 3,4-dimethoxy-6,β-dinitrostyrene has been described. This indole has been converted to a dimethoxy substituted harman, yobyrone, heteroauxin and tryptophan by the application of methods used to prepare the parent substances.

In connection with a problem in alkaloid chemistry a dimethoxy substituted harman I, a similarly substituted yobyrine II, and a series of other compounds related to 5,6-dimethoxyindole (III) were required.



I, R = $-CH_3$



II, R = CH_3

An attempt to prepare I by Perkin and Rubenstein[1] in 1926 by the Fischer indole method was abandoned because of the extreme instability of the intermediate 3,4-dimethoxyphenylhydrazine. The synthesis of 5,6-dimethoxyindole (III) from 6-nitrohomoveratrole by the Reissert method has been reported by Oxford and Raper.[2] In seeking a more convenient route to III, the starting point for our further transformations, we investigated the Nenitzescu synthesis which has been successfully exploited by Robertson and co-workers[3] in a study of the chemistry of melanins. Nitration of veratraldehyde in the 6-position[4] and conversion to 3,4-dimethoxy-6,β-dinitrostyrene (IV) by reaction with nitromethane proceeded easily and in satisfactory yield. The reduction and ring closure of IV to produce the indole III, when carried out in the usual manner, employing iron powder and a large excess of acetic acid, worked satisfactorily only on the small scale (2 g.) used by Robertson.[3] Increasing the scale caused a drop in yield and made the work-up of the reaction mixture excessively tedious. We investigated the optimum conditions for the conversion of IV to III by catalytic reduction, a hitherto undescribed variation of the Nenitzescu synthesis. Using palladium-on-carbon as a catalyst in an ethyl acetate–ethanol solvent mixture in the presence of four molar equivalents of acetic acid to remove the ammonia formed, 60% yields of III were obtained regardless of the scale of the reaction.

The route from III to 3-(2-aminoethyl)-5,6-dimethoxyindole (V) followed the sequence used by Thesing and Schülde[5] in their excellent tryptamine synthesis. Thus, III was converted successively to 3-(dimethylaminomethyl)-5,6-dimethoxyindole (VI), to the quaternary salt of VI and to 5,6-dimethoxyindole-3-acetonitrile (VII). High pressure catalytic reduction of VII gave the substituted tryptamine (V). Transformation of V to I proceeded according to the pattern of the harmala synthesis of Späth and Lederer.[6] Ring closure with phosphorus pentoxide of VIII (obtained either by acetylation of V or by the reduction of VII in acetic anhydride over platinum) afforded 3,4-dihydro-6,7-dimethoxy-1-methyl-9H pyrid[3,4-b]-indole (IX). In the final step 6,7-dimethoxy-1-methyl-9H-pyrid[3,4-b]indole (I) (7,8-dimethoxy-2-methyl-β-carboline) was obtained by catalytic dehydrogenation of IX. Compounds were also required in which the pyridine ring of I was completely reduced. Two of these (X and XI) were obtained by catalytic reduction of IX and by so-

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(2) A. E. Oxford and H. S. Raper, *ibid.*, 417 (1927).
(3) R. J. S. Beer, K. Clarke, H. F. Davenport and A. Robertson, *ibid.*, 2029 (1951).
(4) A. H. Salway, *ibid.*, **95**, 1155 (1909).
(5) J. Thesing and F. Schülde, *Ber.*, **85**, 324 (1952).
(6) E. Späth and E. Lederer, *ibid.*, **63**, 2101 (1930).