of tris-(chloromethyl)-acetic acid, presumably a new compound.

3. The action of hot quinoline on tris-(chloromethyl)-acetic acid gave a good yield of 3-chloro-2-(chloromethyl)-1-propene, whose structure is supported by its saponification to give the corresponding glycol.

TROY, NEW YORK RECEIVED MARCH 13, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

Conversion of D(+)-Acetone Glycerol into its Enantiomorph

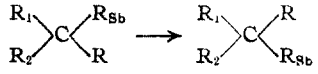
BY ERICH BAER AND HERMANN O. L. FISCHER

In principle any optically active substance whose asymmetry is due to substitution in one of two otherwise identical groups can be converted into its antipode by interchanging the position of the substituent (Scheme A).

E. Fischer and Brauns[1] succeeded in exchanging the position of the hydroxyl and amide group of the dextro-rotatory isopropylmalonamidic acid and obtained the levo-rotatory isomer with practically no loss in optical activity. This successful conversion is still regarded as an excellent experimental confirmation of the spatial concept of the asymmetric carbon atom as postulated by van't Hoff and Le Bel.

In 1937 the authors reported in a preliminary note, without giving experimental details,[2] the conversion of D(+)-acetone glycerol into L(−)-acetone glycerol. The levo-rotatory isomer was obtained by transposing the acetone group. The directing of this group into its new position and the maintenance of the optical activity of the molecule during the six steps of the conversion were accomplished by a series of asymmetric substitutions of the glycerol molecule as shown in Scheme B which also illustrates the steric relationships of the intermediary compounds.

SCHEME A

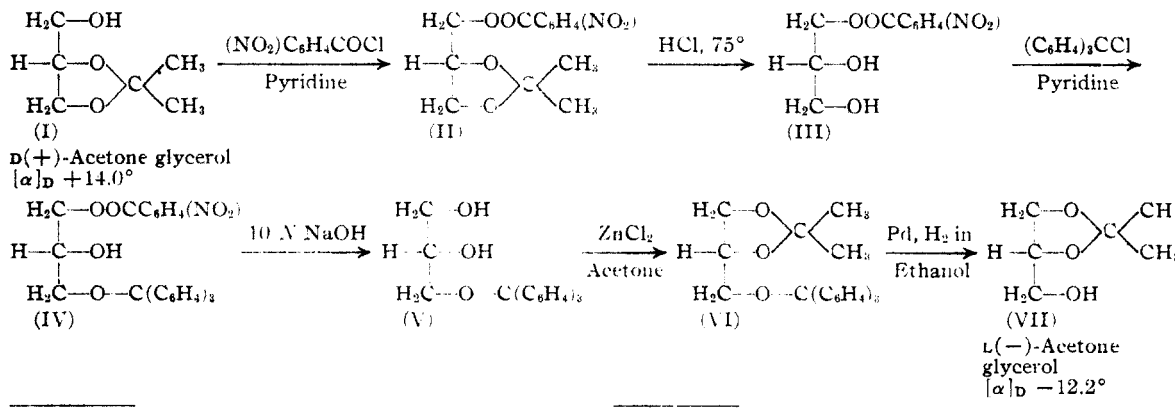


D(+)-Acetone glycerol (I) was nitrobenzoylated in pyridine and the resulting nitrobenzoate (II) was deacetonated in 0.5 *N* hydrochloric acid at 75 to 80°. The tritylation of L-(*p*-nitrobenzoyl) glycerol (III) in pyridine gave L-(*p*-nitrobenzoyl)-glycerol-trityl ether (IV). Saponification of IV with sodium hydroxide in ethanol yielded D-glycerol-trityl ether (V) which on acetonation with zinc chloride in acetone formed L-(−)-acetone glycerol-trityl ether (VI).[3] Catalytic removal of the trityl group in compound VI with hydrogen in the presence of palladium on charcoal resulted in the formation of L(−)-acetone glycerol (VII) which was identical with L(−)-acetone glycerol prepared from L-mannitol.[4]

Because of the numerous reactions involved, the L(−)-acetone glycerol was obtained in a yield of 6.6% only. Its optical activity was 12.5% less than that of D(+)-acetone glycerol. This small loss in optical activity must have occurred during detritylation, since the rotation of L(−)-acetone glycerol-trityl ether prepared by tritylation of L(−)-acetone glycerol is the same as that of L(−)-acetone glycerol-trityl ether obtained by conversion.

Early in our work dealing with the synthesis of optically active glycerides,[5] the need for L(−)-acetone glycerol as a starting material for the synthesis of the D-series of α-mono-glycerides arose and its preparation from D(+)-acetone glyc-

SCHEME B



(1) E. Fischer and F. Brauns, *Ber.*, **47**, 3181 (1914); *cf.* Henry Gilman, "Organic Chemistry," second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. I, p. 227.

(2) *Naturwissenschaften*, **25**, 588 (1937).

(3) Another method of preparation of this compound by tritylation of L(−)-acetone glycerol is also described in the experimental part.

(4) E. Baer and H. O. L. Fischer, THIS JOURNAL, **61**, 761 (1939).

(5) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 475 (1939)

erol by conversion was considered. About this time, however, L(−)-acetone glycerol was found to be more readily obtainable via L-mannitol.[4] Although the conversion of D(+)-acetone glycerol into L(−)-acetone glycerol actually never became a necessity in order to obtain the latter substance for synthetic purposes, the interest in the conversion from a theoretical point of view remains. The sequence of reactions described is, as far as the authors are aware, the second example of an enantiomorphic conversion by exchange of substituents.

Experimental Part

(*p*-Nitrobenzoyl) D(+)-Acetone Glycerol (II).—Twenty-six and four-tenths grams of freshly prepared D(+)-acetone glycerol[6] ($[\alpha]^{22}D$ + 14.0°) was added drop by drop from a separatory funnel to a gently agitated mixture of 37.1 g. of *p*-nitrobenzoyl chloride in 180 cc. of dry pyridine, over a period of ten minutes. During the addition the pyridine solution was kept at −10°. After standing for twenty hours at room temperature, the pyridine solution was poured with stirring into two liters of distilled water. The clear supernatant liquid was decanted and the residue was dissolved in ether. The ether solution was washed quickly first with small volumes of ice-cold 2 *N* sulfuric acid until the wash water was slightly acid, then with a saturated aqueous solution of sodium bicarbonate and finally with water. The ether solution was dried with anhydrous sodium sulfate and concentrated to a volume of 140 cc. This solution was kept for several hours at −70°. The *p*-nitrobenzoate was filtered with suction on a cooled Buchner funnel and dried in a high vacuum at room temperature; yield 47.0 g. (83.5%). After recrystallizing the substance from a small volume of dry ether at −60°, the acetone compound melted at 36.5–37.0°; $[\alpha]^{22}D$ +5.8°, for c = 10.3 in dry pyridine. *Anal.* Calcd. for $C_{13}H_{15}O_6N$ (281.1); C, 55.51; H, 5.39; N, 4.98. Found: C, 55.50; H, 5.18; N, 4.86.

L-(*p*-Nitrobenzoyl) Glycerol (III).—A vigorously stirred suspension of 47.0 g. of the acetone compound in 600 cc. of 0.5 *N* hydrochloric acid was kept in a water-bath at 75–80° for a period of fifty minutes. The clear solution, on cooling to room temperature, precipitated 30.9 g. (76.5%) of nitrobenzoate. Recrystallization from 180 cc. of boiling chloroform yielded 26.1 g. of pure L-(*p*-nitrobenzoyl) glycerol, m. p. 87–88°; $[\alpha]^{22}D$ −16.4°, for c = 10.2 in dry pyridine, $[\alpha]^{23}D$ −18.4°, for c = 10.2 in dry ethanol. *Anal.* Calcd. for $C_{10}H_{11}O_6N$ (241); C, 49.77; H, 4.60. Found: C, 49.55; H, 4.6.

L-(*p*-Nitrobenzoyl) Glycerol-trityl Ether (IV).—To an ice-cold solution of 30.2 g. of pure triphenylchloromethane[7] in 110 cc. of dry pyridine was added 26.1 g. of L-(*p*-nitrobenzoyl)-glycerol. After standing for two days at room temperature, the pyridine solution was poured into 1000 cc. of ice-cold water and the mixture stirred until the supernatant liquid had become almost clear. The aqueous solution was decanted and the precipitate was washed by triturating twice with 150 cc. of water. The residue was dissolved in 500 cc. of ether, washed in rapid succession three times with 50 cc. of ice-cold 1 *N* sulfuric acid, once with 50 cc. of a saturated aqueous solution of sodium bicarbonate and twice with 50 cc. of water. The ether solution was dried with anhydrous potassium carbonate and concentrated by distilling off most of the ether. During concentration a part of the trityl compound crystallized out and was filtered off. The rest was obtained by permitting the ethereal mother liquor to evaporate slowly in an open dish; total yield 42.8 g. (81.6%) of crude *p*-nitrobenzoyl-trityl glycerol melting from 115–125°. For purification the substance was recrystallized from 200 cc. of warm *n*-butyl ether; yield 34.4 g. of pure glycerol derivative, m. p. 135–136°; $[\alpha]^{22}D$ −5.7°, for c = 10.3 in *s*-tetrachloroethane. *Anal.* Calcd. for $C_{29}H_{25}O_6N$ (483); C, 72.1; H, 5.22; sapn. no., 116.2. Found: C, 72.1; H, 5.57; sapn. no. 113.1.

D-Glycerol-trityl Ether (V).—34.4 grams of (*p*-nitrobenzoyl)-glycerol-trityl ether was dissolved in 450 cc. of warm 99% ethanol. The solution was cooled to room temperature and 75 cc. of 10 *N* sodium hydroxide added. After standing for twenty-four hours, the solution was diluted with 1000 cc. of ether, washed with water until colorless and free from alkali and concentrated to approximately 200 cc. After removing the rest of the solvent in an air current, a crystalline sludge was obtained which on filtering with suction yielded 21.75 g. (91.4%) of D-glycerol-trityl ether. Recrystallization from 200 cc. of boiling isopropyl ether raised the melting point from 93 to 97°; $[\alpha]^{22}D$ +3.4°, for c = 6.0 in *s*-tetrachloroethane, $[\alpha]^{22}D$ −17.7°, for c = 8.0 in dry pyridine. *Anal.* Calcd. for $C_{22}H_{22}O_3$ (334.2); C, 78.99; H, 6.63. Found: C, 78.81; H, 6.65. *Glycol No.*[8] Calcd., 1326.0. Found: 1293.0 (97.5%).

L(−)-Acetone Glycerol-trityl Ether (VI).—Fifty grams of anhydrous zinc chloride was dissolved in 250 cc. of dry acetone. After permitting the undissolved zinc salts to settle out the solution was quickly decanted. In 210 cc. of this solution was dissolved 21.75 g. of D-glycerol-trityl ether and the mixture, protected from moisture, was kept twenty-four hours at room temperature. At the end of this time the solution was poured quickly into a vigorously stirred solution of 72 g. of anhydrous potassium carbonate in 72 cc. of water which was covered with 300 cc. of ether. The stirring was continued for thirty minutes. The ether–acetone solution was decanted, the zinc carbonate was washed several times with small amounts of ether and the combined solutions were dried with anhydrous potassium carbonate. After distilling off most of the ether, the concentrate was brought to dryness in an air current and the residue was dried in a high vacuum over potassium hydroxide at room temperature; yield 21.8 g. (89.5%) of crude acetone glycerol-trityl ether; m. p. 60 to 72°. The substance was freed from triphenylcarbinol by dissolving in approximately 550 cc. of petroleum ether (b. p. below 40°), filtering off the carbinol and evaporating the filtrate to dryness in a current of air. The residue (19 g.) recrystallized from 15 cc. of butyl ether yielded 14.4 g. of analytically pure L(−)-acetone glycerol-trityl ether, m. p. 85–86°; $[\alpha]^{23}D$ −13.5°, for c = 10.0 in *s*-tetrachloroethane. *Anal.* Calcd. for $C_{25}H_{26}O_3$ (374.2); C, 80.17; H, 7.00. Found: C, 80.4; H, 7.00.

L(−)-Acetone Glycerol (VII).—A suspension of 5 g. of palladium-charcoal[9] catalyst and 1.0 g. of pure barium carbonate in a solution of 7.48 g. of L(−)-acetone glycerol-trityl ether in 60 cc. of dry ethanol was shaken at room temperature (22°) in an atmosphere of dry hydrogen ($CaCl_2$-tube) of approximately 30 cm. of water pressure until the absorption of hydrogen ceased (*ca.* twenty hours). After replacing the hydrogen by nitrogen, the mixture was filtered with suction and the clear filtrate concentrated under diminished pressure at a bath temperature of 20°. The crystalline sludge was dissolved in 30 cc. of dry ether and dried overnight with anhydrous potassium carbonate. The ether solution was decanted, the carbonate washed three times with small volumes of dry ether and the combined ether solutions were evaporated in a flask with sealed-on receiver.[10] The L(−)-acetone glycerol was separated from the triphenylmethane by distilling *in vacuo;* yield 0.90 g. (34.6%), b. p. (8 mm.) 72–73° (bath 85–90°); $n^{23}D$ 1.4335, $[\alpha]^{22}D$ −12.2°, in substance, d^{22}_4 1.062.

(6) Prepared according to the simplified procedure reported by us in the *J. Biol. Chem.*, **128**, 463 (1939); Raney nickel was used as a catalyst.

(7) The triphenylchloromethane was purified by distillation in a high vacuum, b. p. (0.05 mm.) 150–160° (bath 170–180°)

(8) Defined as the weight of lead tetraacetate in milligrams used for the oxidative cleavage of one gram of the compound.

(9) Ott and Schröter, *Ber.*, **60**, 633 (1927); Hartung, THIS JOURNAL, **50**, 3370 (1928).

(10) E. Baer, *Ind. Eng. Chem., Anal. Ed.*, **16**, 399 (1944).

L(−)-Acetone Glycerol-trityl Ether. (Compound prepared by tritylation of L(−)-acetone glycerol.)—To a cold solution of 27.8 g. of triphenylchloromethane[7] in 90 cc. of dry pyridine was added 13.2 g. of freshly prepared L(−)-acetone glycerol ($[\alpha]_D$ −13.8°) and the mixture permitted to stand for two days at room temperature. The mixture was poured into 800 cc. of ice-water and stirred until most of the trityl compound had settled out. The aqueous solution was decanted and extracted once with 500 cc. of ether. This extract was used to take up the trityl compound adhering to the walls of the beaker. The solution was washed four times with 200 cc. of water and dried with anhydrous potassium carbonate. The ether solution was decanted, concentrated and the residual ether was removed in a current of air. The last traces of pyridine were removed by keeping the substance in a high vacuum over phosphorus pentoxide and sodium hydroxide; yield 34.8 g. (93.2%) of crude L(−)-acetone glycerol-trityl ether, m. p. 67–81°. The substance was purified by recrystallization from butyl ether: 34.8 g. of the trityl ether was dissolved in 25 cc. of warm butyl ether and the solution kept overnight in an ice box. After draining off the mother liquor, the crust of crystals was broken up and the rest of the mother liquor removed by spreading the substance on a porous plate: 25.3 g. (67.8%) of analytically pure L(−)-acetone glycerol-trityl ether with a melting point of 85–86° was obtained; $[\alpha]^{23}$ −13.0°, for c = 10.0 in *s*-tetrachloroethane.

Summary

The conversion of D(+)-acetone glycerol into L(−)-acetone glycerol has been accomplished by means of a sequence of substitution reactions.

The transposition described offers a further example of an enantiomorphic interconversion by exchange of substituents.

TORONTO, CANADA RECEIVED MARCH 22, 1945

[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of Arsonoanilinopyrimidines

BY RAYMOND J. ANDRES AND CLIFF S. HAMILTON

The discovery by Friedheim,[1] that 2-(4′-arsonoanilino)-4,6-diamino-*s*-triazine far exceeded tryparsamide as an agent in the treatment of African trypanosomiasis, provided a new approach in the search for arsenicals effective in combatting such diseases. Banks and co-workers,[2] in extending the work of Friedheim to other arsonic acid derivatives of *s*-triazine, found that the *p*-arsonanilino derivative, further substituted in the heterocyclic nucleus by an amino group, and a hydroxyl group is a very active therapeutic agent.

Since pyrimidine is closely related in structure to *s*-triazine, the present work was concerned with the synthesis of arsonoanilino derivatives of pyrimidine in which the heterocyclic nucleus was substituted by amino, hydroxyl and thioether groups.

From the mechanism proposed by Banks[3] it could be predicted that a halogen on the 2, 4, or 6 carbon atom of the pyrimidine nucleus would have its known activity toward replacement by an amino group increased in the presence of hydrogen ions. Consequently, a group of 2- or 4-chloropyrimidines was selected, each member being further substituted by amino, nitro, methyl, or ethyl mercapto groups. Those chosen reacted with aminophenylarsonic acids in the presence of dilute, aqueous acid.

In the study of the action of hydrogen peroxide on 2-ethylmercapto-4-(4′arsonoanilino)-6-methylpyrimidine, in an aqueous solution buffered by sodium bicarbonate, the sulfone was not obtained. Analysis indicated that the ethylmercapto group had been replaced by the hydroxyl group, a hypothesis substantiated in part by the absence of sulfur from the molecule. The use of hydrochloric acid or hydrobromic acid to effect a similar replacement is reported in the literature.[4,5] Alkaline peroxide has the advantage over previous methods in that it does not seriously affect the anilinopyrimidine linkage.

Experimental

All melting points were corrected for exposed stem. A thermometer calibrated by the Bureau of Standards was used.

Materials Used

2-Amino-4-chloro-6-methylpyrimidine was prepared according to the method of Gabriel and Colman.[6] For the preparation of **2-amino-4,6-dichloropyrimidine** the method of Büttner[7] was used. **2-Ethylmercapto-4-chloro-6-methylpyrimidine** was synthesized according to the directions of Johns,[8] while Roblin, *et al.*,[9] were followed in the preparation of **2-chloro-5-nitropyrimidine.** ***p*-Arsanilic acid** was purified by twice recrystallizing the technical grade from dilute alcohol. The directions of Stevinson and Hamilton[10] were followed for the reduction of *m*-nitrophenylarsonic acid to ***m*-arsanilic acid.** Parke, Davis and Company kindly furnished the two **aminohydroxyphenylarsonic acids** and **2-amino-4-chloropyrimidine.**

General Procedure.—One equivalent of the aminophenylarsonic acid was dissolved in boiling water containing 0.1 to 1.2 equivalents of hydrochloric acid, 50 ml. of water or a water–organic solvent mixture being present for each gram of arsonic acid. To the boiling solution was added 1.2 to 2.0 equivalents of the chloropyrimidine. The mixture was refluxed until a qualitative test with "R" acid showed the absence of the primary amino group. The hot solution was then made neutral to congo red paper and the product filtered off hot. Purification was effected by

(1) Friedheim, *Schweiz. Med. Wochschr.*, **5**, 116 (1941).

(2) Banks, Gruhzit, Tillitson and Controulis, THIS JOURNAL, **66**, 1771 (1944).

(3) Banks, *ibid.*, **66**, 1127, 1131 (1944).

(4) Wheeler and Jamieson, *Am. Chem. J.*, **32**, 342 (1904).

(5) Chi and Kao, THIS JOURNAL, **58**, 772 (1936).

(6) Gabriel and Colman, *Ber.*, **32**, 2921 (1899).

(7) Büttner, *ibid.*, **36**, 2227 (1903).

(8) Johns, *Am. Chem. J.*, **40**, 348 (1908).

(9) Roblin, Winnek and English, THIS JOURNAL, **64**, 567 (1942).

(10) Stevinson and Hamilton, *ibid.*, **57**, 1298 (1935).