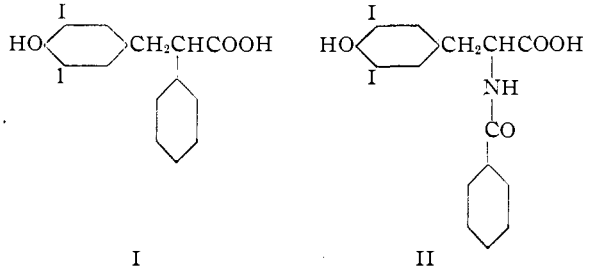
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, IOWA STATE COLLEGE]

Amino Acid Conversion Products. III. 3,5-Diiodotyrosine Derivatives

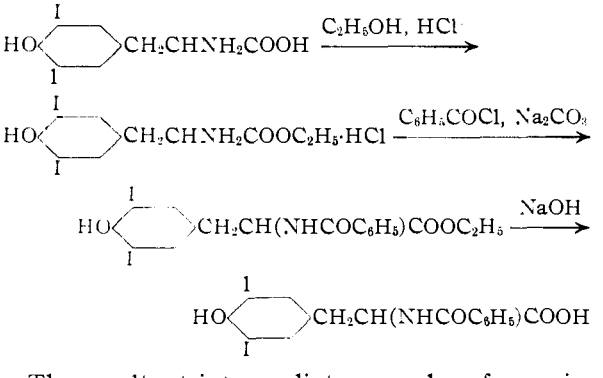
BY SIDNEY W. FOX

Since diiodotyrosine may be prepared from one of the amino acids which is available in quantity, the possible synthesis of radio-opaque derivatives is of interest. The structurally related compound, β-(4-hydroxy-3,5-diiodophenyl)-α-phenylpropionic acid, I, has been used medically as a cholecystographic agent (*Priodax*, *Selectan*). Whereas diiodotyrosine is physiologically active, its N-benzoylated derivative, II, does not liberate inorganic iodine metabolically, and the latter compound does not have the physiological activity of diiodotyrosine.[1] The requirements of physiological inertness are also met in I.



I II

N-Benzoyldiiodotyrosine has not been synthesized by a satisfactory method, nor has it been properly characterized. The compound may be prepared smoothly by the directions given in the experimental part. The reactions involved are



The resultant intermediates are also of experimental pharmacological interest. Another substance of interest in this connection is the amide, obtained by the action of ammonia on the ester.

Experimental

Diiodo-*l*-tyrosine Ethyl Ester Hydrochloride.—Thirty grams of diiodotyrosine prepared[2] from Merck *l*-tyrosine was covered with 500 cc. of absolute ethanol and the mixture saturated with dry hydrogen chloride. The fine needles which separated on chilling weighed 20 g. when dry. A sample decomposed at 217–218° (uncor.) with prebrowning. On recrystallization from five parts of 95% ethanol a sample decomposed at 215–216° (uncor.) with prebrowning and had $[\alpha]^{D}_{27}$ +18.7 ± 0.2° when 0.775 g. was made up to 10.0 cc. with 95% ethanol.

The mother liquor of the original precipitate was concentrated to dryness, the residue dissolved in 70 cc. of hot absolute ethanol, and the solution treated with 200 cc. of ether and 300 cc. of hexane. There was recovered 9.5 g. of precipitate, of which a sample decomposed at 216–217° (uncor.). The total yield was 29.5 g. (85%). The ninhydrin test was negative for this material.

Anal. Calcd. for $C_{11}H_{14}O_3NClI_2$ (497): N, 2.8. Found: 2.8.

Diiodo-*l*-tyrosine Ethyl Ester.—To 7.2 g. of powdered ester hydrochloride suspended in 60 cc. of water was added with shaking 30 cc. of 2 *N* sodium carbonate solution. The solid was filtered and washed copiously with water. After drying in air it weighed 6.2 g. A sample melted 179–180° (uncor.) with decomposition and this melting point was unchanged after recrystallization from 50 parts of chlorobenzene.

Anal. Calcd. for $C_{11}H_{13}O_3NI_2$ (461): N, 3.0. Found: 3.1.

This compound has been obtained previously by iodination of ethyl tyrosinate.[3]

N-Benzoyl-*l*-diiodotyrosine Ethyl Ester.—Ten grams of powdered ester hydrochloride was shaken with 10 cc. of water, 40 cc. of 2 *N* sodium carbonate solution and 200 cc. of chloroform in a separatory funnel. To this was added 2.3 cc. of benzoyl chloride in four portions, the mixture being shaken vigorously after each addition and until no more carbon dioxide evolved, at which time there was practically no more solid phase. The chloroform layer was then filtered and the clear filtrate allowed to evaporate. The yield was 10.5 g. (92%); a sample melted at 153° (uncor.). The solid was recrystallized from 200 cc. of benzene. There was recovered 9.8 g. of m. p. 153° (uncor.). This appeared as dense bundles of very fine needles under the microscope. The presence of the ester grouping in this compound was verified by identification of the ethanol obtained by saponification in diethylene glycol.[4] The distillate after saponification of 2.0 g. of ester yielded approximately 0.2 cc. of ethanol, identified as the 3,5-dinitrobenzoate.

The compound was not readily soluble in warm sodium bicarbonate solution. $[\alpha]^{D}_{26}$ +12.9 ± 0.3° for 0.797 g. dissolved in 2 *N* sodium hydroxide solution to a volume of 10.0 cc.

Anal. Calcd. for $C_{18}H_{17}O_4NI_2$ (565): N, 2.5. Found: 2.4.

N-Benzoyl-diiodotyrosyl Amide.—Four grams of the ester was dissolved in 30 cc. of alcohol with warming and treated with 125 cc. of concentrated ammonium hydroxide. After three days the precipitated solid was filtered off. It weighed 2.0 g. After recrystallization from 18 parts of boiling alcohol samples of various preparations decomposed in the range of 234–248° (uncor.). Within the limits of experimental error, 0.5285 g. in 1 *N* sodium hydroxide solution exhibited no optical activity. A sample of the compound evolved ammonia when heated in boiling 1 *N* sodium hydroxide solution.

Anal. Calcd. for $C_{16}H_{14}O_3N_2I_2$ (536): N, 5.2. Found: N, 5.4.

N-Benzoyl-*l*-diiodotyrosine.—To 9 cc. of 5 *N* sodium hydroxide was added 5.1 g. of the ester and the mixture heated in a boiling water-bath for thirty minutes. The

(1) Snapper and Grunbaum, *Brit. J. Exptl. Path.*, **18**, 401 (1937).
(2) Savitskii, *J. Gen. Chem.* (U. S. S. R.), **9**, 1342 (1939).
(3) Bauer and Strauss, *Ber.*, **68**, 1111 (1935).
(4) Redemann and Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

solution was then diluted with 50 cc. of water and acidified with 20 cc. of 3 *N* hydrochloric acid solution. There was obtained 5.0 g. of solid of indefinite melting point. This was recrystallized from 200 cc. of aqueous ethanol (1:1). Four grams (82%) of well-formed needles was obtained. Samples melted at 186–187° (uncor.) with much preshrinking. The melting point given by Snapper and Grunbaum[1] is 179°. The acid was readily and completely soluble in warm sodium bicarbonate solution (compare Fischer and Lipschitz[5] for behavior of a related acid and ester) and was not appreciably soluble in chloroform. A sample of the compound failed to give a ninhydrin test. In contrast to this behavior, both diiodotyrosine and the methyl ether of tyrosine[6] gave positive ninhydrin reactions.

Anal. Calcd. for $C_{16}H_{13}O_4NI_2$ (537): N, 2.6. Found: N, 2.5; equivalent wt. by titration (methyl red), 536 ± 1.

(5) Fischer and Lipschitz, *Ber.*, **48**, 374 (1915).

(6) Behr and Clarke, THIS JOURNAL, **54**, 1630 (1932).

$[\alpha]^{D}_{27}$ +10.9° ± 0.3° for 0.607 g. dissolved in 0.5 *N* sodium hydroxide solution to 10.0 cc. After a second recrystallization, $[\alpha]^{D}_{27}$ = +10.6 ± 0.7° for 0.671 g. dissolved in 0.5 *N* sodium hydroxide solution to 10.0 cc.

Thanks are due Miss Velma Ladwig and Mr. Luther Eggman for Kjeldahl analyses.

Summary

The synthesis of a number of derivatives of diiodotyrosine for testing as radio-opaque pharmaceutical compounds, is described. Details are given for the conversion of diiodotyrosine to N-benzoyldiiodotyrosine through some of these intermediates in better than 60% over-all yield.

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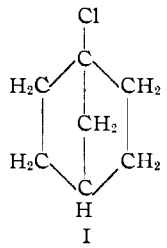
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF UNIVERSAL OIL PRODUCTS COMPANY]

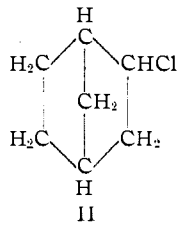
The Exchange of Hydrogen and Chlorine between Bicyclo(2,2,1)heptane and *t*-Butyl Chloride

BY LOUIS SCHMERLING

The hydrogen-chlorine exchange reaction[1] of bicyclo(2,2,1)heptane (also called norcamphane) with *t*-butyl chloride was investigated because it seemed to offer a convenient means for preparing the tertiary chloride, 1-chlorobicyclo(2,2,1)heptane (I), and thence (by condensation with olefins[2]) bicycloheptylalkyl chlorides containing quaternary carbon atoms.



I



II

Bartlett, Condon and Schneider[1] reported that poorly characterized products were obtained by the reaction of bicyclo(2,2,1)heptane with alkyl halides in the presence of aluminum chloride or aluminum bromide. Their general procedure consisted in shaking a mixture of the reactants and the catalyst at room temperature in a separatory funnel for a period of time varying from ten seconds to several minutes and then stopping the reaction either by separating the catalyst layer or by adding water. In the present investigation it was found that smooth transfer of chlorine from *t*-butyl chloride to bicycloheptane can be accomplished in the presence of aluminum chloride by using lower reaction temperatures (about 0°) and longer contact times (thirty to sixty minutes). Chlorobicycloheptane was obtained in 22–24% of the theoretical yield based on the bicycloheptane charged or in 74–84% yield based on unrecovered bicycloheptane. However, the chloride was not the expected tertiary compound but was instead the secondary isomer, 2-chlorobicyclo(2,2,1)heptane (II), which was also obtained by adding hydrogen chloride to bicyclo(2,2,1)-2-heptene. Its structure was further proved by hydrolyzing it to 2-hydroxybicyclo(2,2,1)heptane, better known as β-norcamphanol. β-Norcamphanyl ether was obtained as a by-product of the hydrolysis.

The fact that the bicycloheptane yields a secondary chloride is significant since it indicates that this hydrocarbon differs from those previously studied[1] in that a hydrogen atom attached to a secondary carbon atom rather than one attached to a tertiary carbon atom is involved in the exchange reaction. This non-formation of the tertiary bicycloheptyl compound may be explained as being due to the impossibility in this case of forming the intermediate tertiary carbonium ion as postulated by the mechanism of Bartlett and his co-workers.[1] The tertiary bicycloheptyl carbonium ion presumably cannot exist because the central carbon atom and the three carbon atoms forming bonds with it cannot be coplanar.[3]

Experimental

Reaction of Bicyclo(2,2,1)heptane with *t*-Butyl Chloride.—A solution of 52 g. (0.54 mole) of the bicycloheptane (prepared according to the directions given by Thomas),[4] 52 g. (0.56 mole) of *t*-butyl chloride and 25 g. of *n*-pentane diluent was placed in a large test-tube of such dimensions

(1) P. D. Bartlett, F. E. Condon and A. Schneider, THIS JOURNAL, **66**, 1531 (1944).

(2) For a description of the condensation of alkyl halides with, for example, ethylene see L. Schmerling, *ibid.*, **67**, 1152 (1945).

(3) P. D. Bartlett and L. H. Knox, *ibid.*, **61**, 3184 (1939).

(4) C. L. Thomas, *Ind. Eng. Chem.*, **36**, 310 (1944).