ride[6] has been used before; the application of diethyl phthalimidomalonate gives an over-all yield of 50% (calculated on *p*-fluorobenzyl chloride).

Experimental Part

p-Amino- from p-Nitrophenylalanine.—When 8 g. of the nitro compound[1] (from *t*-butyl alcohol, m.p. 240–245° (dec.)) in 150 ml. of water, was hydrogenated at room temperature and atmospheric pressure, in the presence of 0.8 g. of 5% palladium–barium sulfate as catalyst, the theoretical amount of hydrogen was absorbed rapidly. The filtered solution was concentrated at 50° *in vacuo*, until crystallization set in. Upon cooling, 5.9 g. (87%) of the amino acid was obtained in form of fine needles.

Azlactone of α-Benzoylamino-p-nitrocinnamic Acid.—A mixture of 40 g. (1/6 mole) of hippuric acid, 82 g. (1/6 mole) of anhydrous sodium acetate, 25 g. (1/6 mole) of *p*-nitrobenzaldehyde and 102 g. (1 mole) of acetic anhydride was heated on the steam-bath for 45 minutes, with occasional shaking. The excess of the acetic anhydride was destroyed by treatment with water and the product filtered, thoroughly washed with hot water, and dried at 100°. It was recrystallized from toluene, forming yellow needles of m.p. 242° (lit. 233°,[4a] 239°,[4b] yield 45 g. (91.8%, lit. 76%[4a]).

p-Aminophenylalanine.—The mixture of 29.4 g. of the azlactone, 200 ml. of glacial acetic acid, 500 g. of hydriodic acid (sp. gr. 1.7) and 20 g. of red phosphorus was refluxed for 6 hours, and the hot solution filtered (glass filter) and evaporated *in vacuo* to dryness. The residue was taken up in 200 ml. of water and evaporated again *in vacuo* to dryness; during these operations, part of the benzoic acid formed, sublimed over. The residue was dissolved in 100 ml. of water and this solution extracted twice with ether, concentrated *in vacuo* to about 50 ml. and made alkaline (litmus) by the slow addition of concentrated ammonia solution. Crystallization started at once and was completed by cooling. The crystals were collected and washed with 10 ml. of ice-cold water. Recrystallization from boiling water gave colorless needles of the hydrate which lost its water at 140° (*in vacuo*) and showed a m.p. (dec.) of 265° on quick, and of 254° on slow heating (lit. 245–250°[2]); yield 16.9 g. (85.3%).

Anal. Calcd. for $C_9H_{12}O_2N_2 + 1H_2O$: H_2O, 9.1; C, 54.5; H, 7.1; N, 14.1. Found: H_2O, 9.2; C, 54.3; H, 7.0; N, 14.0.

p-Fluorophenylalanine. (a) **Ethyl p-Fluorobenzyl-phthalimidomalonate.**—An intimate mixture of 6.7 g. of *p*-fluorobenzyl chloride[7] (b.p. 75–77° (14 mm.)) and 11.7 g. of ethyl sodiophthalimidomalonate[8] was heated for six hours at 160° and subsequently for 15 minutes at 200°. The product was digested with hot water, cooled and extracted with ether; it formed an oil (15 g., 72%) which could be purified by distillation *in vacuo:* b.p. 245–250° (13 mm.).

Anal. Calcd. for $C_{22}H_{20}NO_6F$: C, 64.2; H, 4.9; N, 3.4. Found: C, 64.2; H, 5.0; N, 3.6.

(b) **N-(o-Carboxybenzoyl)-p-fluorobenzyl-aminomalonic Acid.**—A mixture of 5 g. of the (crude) ester, 5 ml. of alcohol and 14 ml. of 5 *N* sodium hydroxide solution was refluxed for 2 hours; a solid salt precipitated. Addition of 20 ml. of water, and of 2 *N* hydrochloric acid to neutrality, gave a viscous precipitate, which crystallized upon trituration with 30 ml. of concentrated hydrochloric acid; yield 4 g. (87%); from 50% acetic acid, m.p. 165°.

Anal. Calcd. for $C_{18}H_{14}NO_7F$: C, 57.9; H, 3.8; N, 3.8. Found: C, 57.5; H, 4.0; N, 4.1.

(c).—The foregoing acid (4.2 g.) was heated at 100° with 120 ml. of 5 *N* hydrochloric acid for 45 minutes and, after addition of 60 ml. of 10 *N* hydrochloric acid, for two more hours. The filtered solution was evaporated to dryness *in vacuo*, the residue dissolved in a little hot water and ammonia solution added. Upon addition of some alcohol, the amino acid crystallized. From a water–alcohol mixture (3:1), well-shaped needles, m.p. 238–242° (dec.) upon slow heating; when the substance was heated rapidly, the m.p. was higher (previous authors: 263.5–264°,[5] 259–261[6]); yield 1.7 g. (80%).

Anal. Calcd. for $C_9H_{10}NO_2F$: C, 59.7; H, 5.5; N, 7.7. Found: C, 59.6; H, 5.5; N, 7.8.

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(6) E. L. Bennett and C. Niemann, THIS JOURNAL, **72**, 1800, 1804 (1950).

(7) F. L. M. Pattison and B. C. Saunders, *J. Chem. Soc.*, 2745 (1949).

(8) G. Barger and T. E. Weichselbaum, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 384.

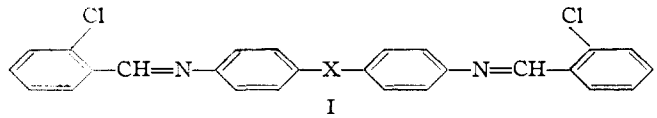
Three Analogs of Bis-(*o*-chlorobenzylidene)-4,4′-diaminodiphenyl Sulfone

BY ERNST D. BERGMANN AND D. LAVIE

RECEIVED MAY 28, 1952

Sah, Oneto, Rohrmann and Kleiderer[1] have shown that the product mentioned in the title (I, X = SO_2) is effective against tuberculosis and have stressed the analogy with the anti-tubercular activity of *o*-chloro substituted benzophenones.[2]

The bis-(*o*-chlorobenzylidene) derivatives of 4,4′-diaminobenzophenone (I, X = CO), 4,4′-diaminodiphenylmethane (I, X = CH_2) and 1,1-di-(*p*-aminophenyl)-2,2,2-trichloroethane (I, X = CH·CCl_3) were prepared and their anti-tubercular activity was tested. The selection of these materials was guided not only by the structural similarity



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with the substituted sulfone, but also by the fact that 1,1-di-(*p*-aminophenyl)-2,2,2-trichloroethane itself inhibits the growth of *M. tuberculosis*[3] and that 4,4′-diaminobenzophenone has been shown by Auhagen[4] and by Kuhn and co-workers[5] to be bacteriostatic against *Streptobacterium plantarum*.

The three substances were tested against a human strain of *Mycobacterium tuberculosis* (Dubos liquid medium No. 2) and proved inactive in the concentration of 10^{-5} g./l.; at 10^{-4} g./l. they showed slight activity.[6]

Experimental

Bis-(o-chlorobenzylidene)-4,4′-diaminodiphenylmethane (I, X = CH_2).—A mixture of 1.5 g. of 4,4′-diaminodiphenylmethane[7] and 2.5 g. of *o*-chlorobenzaldehyde was subjected to azeotropic distillation with 50 cc. of benzene. When no more water appeared in the trap, the solvent was evaporated and the residue recrystallized from glacial acetic acid or butanol; needles, m.p. 135°, yield 3 g.

Anal. Calcd. for $C_{27}H_{20}N_2Cl_2$: N, 6.3. Found: N, 6.5.

Bis-(o-chlorobenzylidene)-4,4′-diaminobenzophenone (I, X = CO).—The mixture of 2.1 g. of the ketone,[8] 2.8 g. of *o*-

(1) P. P. T. Sah, J. F. Oneto, E. Rohrmann and E. C. Kleiderer, *Rec. trav. chim.*, **68**, 141 (1949).

(2) B. L. Freedlander, *Am. Rev. Tuberc.*, **49**, 543 (1944).

(3) A. Burger, E. Graef and M. S. Bailey, THIS JOURNAL, **68**, 1725 (1946); S. Kirkwood, P. H. Phillips and E. McCoy, *ibid.*, **68**, 2405 (1946); S. Kirkwood and P. H. Phillips, *ibid.*, **69**, 934 (1947).

(4) E. Auhagen, *Z. physiol. Chem.*, **274**, 48 (1942).

(5) R. Kuhn, E. F. Moeller, G. Wendt and H. Beinert, *Ber.*, **75**, 711 (1942). The compound and its acetyl derivative are inactive against *Staphylococcus aureus* and *Diplococcus pneumoniae:* M. Asano, T. Yamana and E. Kashiwahbara, *C. A.*, **45**, 5668 (1951).

(6) We are indebted to Dr. David Nachtigall, Tel-Aviv, for these tests.

(7) Preparation by catalytic hydrogenation of 4,4′-dinitrodiphenylmethane.

(8) H. E. Fierz and H. Koechlin, *Helv. Chim. Acta*, **1**, 218 (1918).

chlorobenzaldehyde and 100 cc. of benzene was distilled azeotropically as above. The product (2.5 g.) crystallized from glacial acetic acid; m.p. 144°. *Anal.* Calcd. for $C_{27}H_{18}ON_2Cl_2$: N, 6.1; Cl, 15.5. Found: N, 6.3; Cl, 15.0.

Bis-(*o*-chlorobenzylidene)-1,1-di-(*p*-aminophenyl)-2,2,2-trichloroethane (I, X = ·CHCCl$_3$).—The product of the reaction of 3.15 g. of 1,1-di-(*p*-aminophenyl)-2,2,2-trichloroethane[9] and 2.8 g. of *o*-chlorobenzaldehyde in 100 cc. of benzene was a reddish oil which solidified upon trituration with a small quantity of acetone. The solid (3.2 g.) was recrystallized successively from butanol, methylcyclohexane and glacial acetic acid; m.p. 163–164°. *Anal.* Calcd. for $C_{28}H_{19}N_2Cl_5$: N, 5.0. Found: N, 5.1.

(9) L. Haskelberg and D. Lavie, THIS JOURNAL, **69**, 2267 (1947).

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The β-*p*-Nitrophenylserines and the Corresponding β-*p*-Nitrophenylserinols

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RECEIVED MARCH 19, 1952

Recently Moersch, Rebstock, Moore and Hylander[1] have published a note on the constitution of the β-*p*-nitrophenylserines. We have also investigated this subject and have in press a note on ethyl DL-*erythro*-β-*p*-nitrophenylserinate and its resolution.[2]

Entirely in accordance with the above-mentioned authors we have demonstrated that the ethyl DL-β-*p*-nitrophenylserinate, m.p. 114–115°, obtained by condensation of *p*-nitrobenzaldehyde with ethyl glycinate is of the *erythro* configuration. Starting from Erlenmeyer's β-phenylserine we have also obtained the ethyl DL-β-*p*-nitrophenylserinates, m.p. 130–132°, which we have shown to have the *threo* configuration.[3]

In the above-cited note in press, we have also described the resolution of the ethyl DL-*erythro*-β-*p*-nitrophenylserinate into its optically active forms by means of dibenzoyltartaric acid, with a recovery of the active forms in about 93% yield.[4]

This paper summarizes the results achieved in the selective reduction of *threo*- and *erythro*-β-*p*-nitrophenylserinates with lithium aluminum hydride. Huebner and Scholz[5] starting from the *threo*-N-dichloroacetyl-O-acetyl-*p*-nitrophenylserine ethyl ester obtained by reduction with $LiAlH_4$ a gummy substance which could not be induced to crystallize, but which showed an activity approximately one-half that of chloramphenicol when tested against *S. paradysenteriae*. Bergmann, Bendas and Taub[6] have attempted the reduction with $LiAlH_4$ of ethyl *p*-nitrophenylserinate, but with essentially negative results. Dornow and Winter[7] were the first to attempt the selective reduction of a nitroester. By partial reduction of DL-*p*-nitrophenylalaninate with $LiAlH_4$ they obtained the corresponding alcohol in about 68% yield.

It has been shown by Felkin[8] that the ester group of ethyl *p*-nitrobenzoate and related compounds can be preferentially reduced to the primary alcohol by lithium aluminum hydride without affecting the nitro group.

It is surprising that by selective reduction of the ethyl *erythro*-β-*p*-nitrophenylserinates with $LiAlH_4$, the corresponding *erythro*-*p*-nitrophenyl-2-amino-1,3-propanediols can be obtained in a practically quantitative yield when the quantity of $LiAlH_4$ employed is smaller than the quantity calculated for the blockage of the groups containing active hydrogen (–OH and $-NH_2$) and for the reduction of the ester group; thus with 0.5 mole of $LiAlH_4$ for one mole of ethyl *p*-nitrophenylserinate we obtained a yield of about 60%; with one mole of $LiAlH_4$, the yield was 97% of the theoretical.

We suppose that $LiAlH_4$ in the case of *erythro*-β-*p*-nitrophenylserinates reacts first with the oxygenated functions (–OH and –COOR) and subsequently with the nitrogenated functional groups ($-NH_2$ and $-NO_2$).

We also made an attempt to apply the same selective reduction to ethyl *threo*-DL-β-*p*-nitrophenylserinate and its optical antipodes in order to obtain the corresponding diols. But although the reduction was tried under a variety of conditions, we were unable to obtain the desired diols. Only red oils which gave reactions characteristic of azo compounds are obtained.

Table I summarizes the results of the selective reduction carried out with various amounts of $LiAlH_4$ for one mole of ethyl DL-*erythro*-β-*p*-nitrophenylserinate.

TABLE I

SELECTIVE REDUCTIONS OF ETHYL DL-*erythro*-β-*p*-NITROPHENYLSERINATE

Moles $LiAlH_4$/mole ester	Yield, %	Recovered ester, %
0.25	..	85.0
.50	58.9	40.9
.60	68.4	33.6
.80	80.0	18.8
1.05	97.4	..

Experimental

DL-*erythro*-1-*p*-Nitrophenyl-2-amino-1,3-propanediol.—Ethyl DL-*erythro*-β-*p*-nitrophenylserinate (0.01 mole) dissolved in ethyl ether (500 ml.) was treated in an atmosphere of nitrogen, with finely powdered $LiAlH_4$ suspended in ethyl ether (50 ml.). The addition of the $LiAlH_4$ suspension was carried out at room temperature while stirring for 30 minutes. The mixture was heated for 4 hours in a water-bath at a temperature of 35–40°. The excess of $LiAlH_4$ was then cautiously decomposed by adding 2.5 ml. of water and stirring was continued for another half hour. The mixture was filtered.

The solution was heated on a steam-bath and evaporated to dryness: unchanged DL-*erythro*-β-*p*-nitrophenylserinate if any was recovered.

The residue was transferred to an erlenmeyer flask and 35 ml. of hydrochloric acid was added. The reaction mixture was then heated on a steam-bath until solution was complete. The latter was neutralized with sodium hydroxide to a *p*H of 8–9; then it was extracted seven times with 100 ml. of ethyl acetate. The combined extracts were

(1) G. W. Moersch, M. C. Rebstock, A. C. Moore and D. P. Hylander, THIS JOURNAL, **74**, 565 (1952).

(2) G. Carrara, G. Cristiani, V. D'Amato, E. Pace and R. Pagani, *Gazz. chim. ital.*, in press.

(3) G. Carrara and G. Weitnauer, *ibid.*, **79**, 856 (1949).

(4) G. Carrara and E. Pace, Italian Patent application I6.707 filed on February 5, 1952.

(5) C. F. Huebner and C. R. Scholz, THIS JOURNAL, **73**, 2089 (1951).

(6) E. D. Bergmann, H. Bendas and W. Taub, *J. Chem. Soc.*, 2673 (1951).

(7) A. Dornow and G. Winter, *Ber.*, **84**, 307 (1951).

(8) H. Felkin, *Compt. rend.*, **230**, 304 (1950); **231**, 1316 (1950).