NEW SYNTHESES OF (±) PHENYLALANINOL

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Two synthetic routes of (±) phenyl alanine have been described starting from cinnamyl acetate and 1-phenyl-3-chloro-aceton, resp. In the former case 32%, in the latter 35% yields were achieved.

The discovery of chloramphenicol (I) followed by several syntheses of this potential antibiotic agent stimulated the intensive search for other simpler analogues in several Laboratories [2—24].

Investigations on the synthesis [1] and stereochemistry [43] of I carried out in this Institute at an early date (1949-50) led, as a side reaction, to the synthesis of N-dichloroacetyl phenylalaninol (IIb), a derivative of I without a secondary hydroxyl group in order to establish the contribution of this sensitive

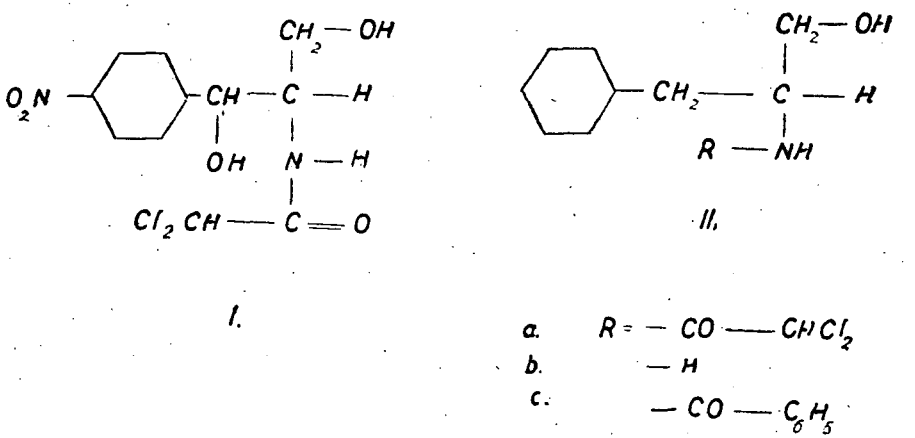

Fig. 1

group to the antibiotic activity of I. On the other hand, the simpler way of preparing this compound could render it preferable to that of I.

Meanwhile plenty of similar syntheses of IIb have already been published using (±) phenylalaninol (IIa) as an intermediate [22], [35—42].

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[1] Part of a thesis submitted to the Faculty of Natural Sciences applying for the title Graduate in Chemistry 1953 and 1954 resp.

This compound has been obtained for the first time from 3-phenyl-DL-alanine by treating it with lithium-aluminium hydride by KARRER [34], who recorded its m. p. 67°—68°. Somewhat later G. FODOR and his co-workers [43]

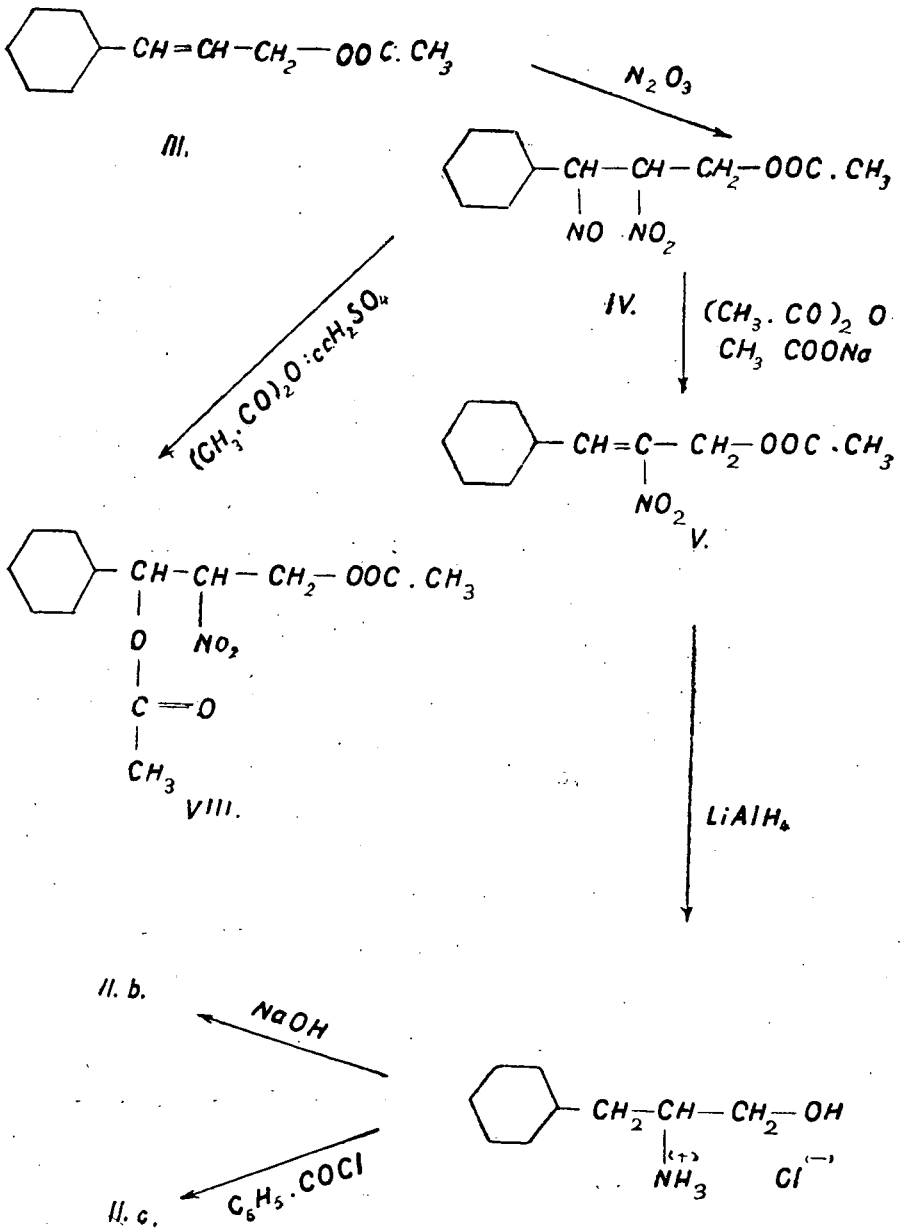

Fig. 2.

described it as an undesired by product in the hydrogenolysis of 1-acetoxy-2-benzamido-3-triphenylmethoxy-propane at pH 7, followed by a stepwise hydrolysis to (±) phenyl-alaninol, m p. 87°—89°.

We wish to record now the preparation of phenylalaninol starting with (1) cinnamyl alcohol (2) phenyl chloromethyl ketone.

Cinnamyl acetate (III) gave on the action of nitrous acid 1-phenyl-1-nitroso-2-nitropropanyl-3-acetate (IV) which, in turn, underwent S_N2 substitution by the action of acetic anhydride in the presence of an electrophilic catalyst (as sulphuric acid) into diacetyl-1-phenyl-2-nitro-propan-1.3-diol (VIII) the key intermediate of a certain synthesis [1] of I. The latter has been accompanied by 1-phenyl-2-nitro-1-propen-3-yl acetate (V) formed as a result of elimination (E 2). Using potassium hydroxide in ethanol, the unsaturated compound became the major product according to BRUCKNER and KRÁMLI [44—46] in the case of some substituted propenylbenzene ψ-nitrosites. Unfortunately, however, this technique does not give any well defined product in our case hence another weaker nucleophil agent: sodium acetate, had to be adopted, which led actually to very good yields of the nitro olephine (V) by an E 2 reaction. This furnished, when hydrogenated by lithium aluminium hydride (±) 1-phenyl-2-amino-3-propanol (IIb) owing to a 1.4-addition of hydrogen to the conjugated system of the 3-phenyl-2-nitro-allyl acetate. The assumed intermediate: benzyl-β-hydroxy methyl-ketoxime, however, escaped isolation as it seems to be hydrogenated to amino-propanol faster than it forms. This result can be reconciled with findings of other authors [47—51] concerning the $LiAlH_4$ reduction of $\alpha\cdot\beta$-unsaturated ketones and $\alpha.\beta$-unsaturated nitro compounds, respectively. (±) Phenylalaninol (IIb) proved identical in every respect with the specimen recorded by Hungarian authors [43].

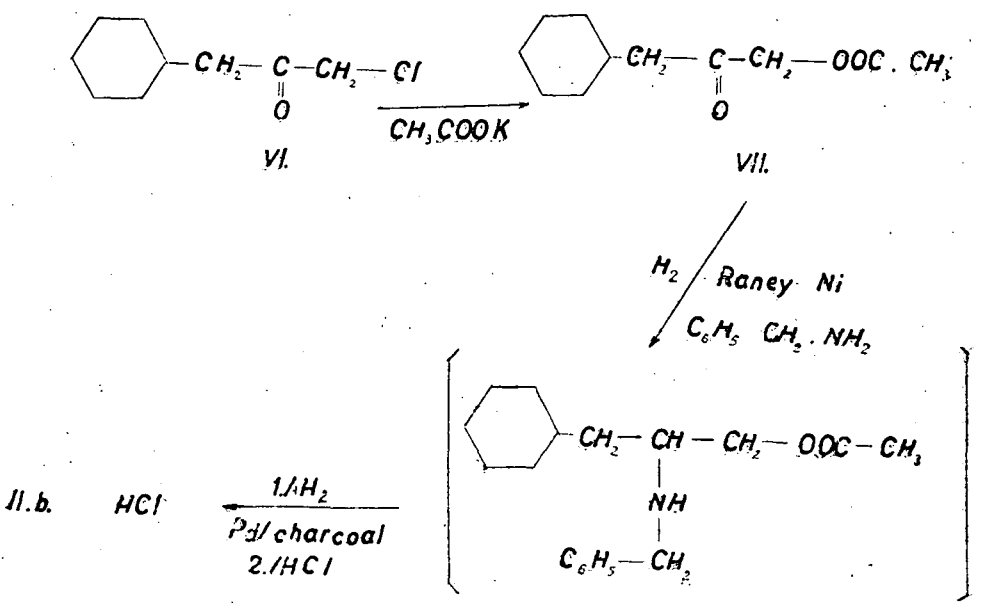

Fig.3

A second route of preparing this compound has been based upon earlier practice collected in synthesizing a series of amino alcohols related to *nor*-adrenaline [25—33]. This approach involved the reductive amination of the ketone whose oxime may serve as an intermediate in our method described above. Benzyl chloromethyl ketone (VI) being readily available [52] it was, in turn, converted by sodium acetate into 1-phenyl-3-acetoxy-acetone [53] (VII), which, underwent reductive condensation with benzylamine over Raney-nickel catalyst to give N-benzyl-phenyl-alaninol. As the last steps, hydrogenolysis of the benzyl group followed by acid hydrolysis of the ester linkage afforded pure (±) phenylalaninol hydrochloride [43] (IIb HCl).

Phenylalaninol (IIb) has been transformed in two further items into deoxy chloramphenicol (IIa) essentially on the lines given by WEITNAUER [23] et al.

Experimental

Cinamyl alcohol acetate (III). Cinamyl alcohol acetate has been prepared according to E. CHERBULIEZ [54] from cinnamyl alcohol by acetic anhydride in the presence of sodium acetate. At the end of the reaction a slight modification of this method was applied, i. e. the formed acetic acid and the half amount of the acetic anhydride were removed by vacuum distillation. Yield 95%; b. $p._2 = 117{,}0^\circ C$.

Erythro-1-phenyl-1-nitroso-2-nitro-3-acetoxy-propane (IV) has been prepared according to FODOR and co-workers [1] from cinnamyl alcohol acetate. Yield: 69%, m. p.: 124°C.

Reaction of erythro-1-phenyl-1-nitroso-2-nitro-3-acetoxy-propane (IV) with ethanolic potassium hydroxide. Erythro-1-phenyl-1-nitroso-2-nitro-3-acetoxy propane (IV) (5.4 g; 0.02 mole) was dissolved in 10% ethanolic potassium hydroxide (24 ml) on shaking at room temperature. This was accompanied by bubbling whilst the solution became brown. After setting aside for ten min., the reaction mixture was acidified with 20% hydrochloric acid, the separated potassium chloride centrifuged and finally the filtrate evaporated to dryness *in vacuo*. Since the brown gummy residue failed to crytallise, its solution in acetic anhydride (10 ml) was reacetylated at 100° for 30 mins. After cooling, it was alkalified by sodium carbonate and extracted with 3×100 ml ether. The ethereal residue was dried (Na_2SO_4), filtered and evaporated to give a brown, sticky remainder (3,4 g), which proved to be amorphous.

dl-1-Phenyl-2-nitro-3-acetoxy-propene-1 (V). To a solution of crystalline sodium acetate (68 g) in glacial acetic acid (400 ml) under mild heating, *dl-erythro*-1-phenyl-1-nitroso-2-nitro-3-acetoxy propane (IV) (25,2 g, 0,1 mole) was portionwise added in 10 mins. in N_2 stream under constant stirring. The reaction mixture was kept at 70°— 80° for further 2 hours and after cooling poured in ice-water (200 ml). This was kept for a few hours at —5° C. The separated crystals were filtered and washed with 50% acetic acid (16,5 g). The crude product was recrystallised from 75% acetic acid (charcoal) giving *dl*-1-phenyl-2-nitro-3-acetoxy propene (V) (12,3 g; 58%) as pale yellow needles, m. p.: 78°—80°. (Found: C 59,62; H 5,15; N 6,43. $C_{11}H_{11}O_4N$ requires: C 59,74; H 4,97; N 6,33%.)

dl-1-Phenyl-2-amino-propanol-3-hydrochloride (IIb HCl). The solution of 1-phenyl-2-nitro-propene-1 (V) (4,42 g; 0,02 mole) in 100 ml of abs. ether was added dropwise in 1 hour to a suspension of $LiAlH_4$ (5,7 g; 0,15 mole) in abs.

ether (250 ml) under mild heating and vigorous stirring. Further stirring was applied for 10 hours at the same temperature. The reaction mixture was allowed to stand for further 12 hours, then the excess of $LiAlH_4$ and the formed complex were decomposed by addition of water under ice-cooling. When the ethereal layer separated from the precipitated $Al(OH)_3$, the precipitate was extracted with warm 96% ethanol (3 × 150 ml), then the combined ethereal and ethanolic solutions were evaporated to afford a pale-coloured oil (3,05 g; 80,5%) which on standing for several days crystallised.

On dissolving in abs. ethanol acidifying with abs. ethanolic HCl (pH 3), concentrating to a small volume and crystallising after the addition of ethylacetate, 2,24 g of the crude product was obtained.

Twice recrystallised from a 1 : 5 mixture of abs. ethanol and abs. ethylacetate: it yielded pure *dl*-1-phenyl-2-aminol-propanol-3-hydrochloride (IIb HCl), m. p.: 139°— 141° [43]. (Found: C 57,42; H 7,85; N 7,72. $C_9H_{14}ONCl$ requires; C 57,6; H 7,45; N 7,45%.)

1-Phenyl-2-benzamido-propanol-3 (IIc). Solid sodium hydroxide (0,92 g; 0,23 mole) was added to a solution of *dl*-1-phenyl-2-amino-propanol-3 hydrochloride (IIb HCl) (1,62 g; 0,01 mole) in water (18 ml); this was followed by the dropwise addition of benzoyl chloride (1,68 g; 0,012 mole) in 10 min. under vigorous stirring. Stirring was continued for further 30 min. Subsequent to extracting with ether (3×50 ml), the ethereal extracts were dried (Na_2SO_4) and evaporated. On recrystallising twice from benzene, pure *dl*-1-phenyl-2-benzamido-propanol-3 (IIc) (1,05 g), m. p. 140°— 150° was obtained. (Found: C 75,15; H 6,84. $C_{16}H_{17}O_2N$ requires: C 75,32; H 6,74%.)

1-Phenyl-2-amino-propanol-3 (IIb). A solution of *dl*-1-Phenyl-2-amino-propanol-3 hydrochloride (IIb HCl) (0,91 g; 0,005 mole) in water (5 ml) was alkalified by 40% sodium hydroxide (1 ml) and extracted with ether (4 × 10 ml). After the ethereal extract had been worked up, the substance thus obtained was recrystallised from benzene-light petroleum to yield pure *dl*-l-phenyl-2-amino-propanol-3 (IIb) (0,52 g), m. p. 87°—88°. On admixture of the authentic specimen prepared by G. FODOR and co-workers [43], no depression of m. p. was observed.

1-Phenyl-3-chloro-acetone (VI). The synthesis of this compound was carried out according the *Organic Syntheses* [52]. Yield: 85% b. p.$_{12}$: 103°—104° C.

1-Phenyl-3-acetoxyacetone (VII). l-Phenyl-3-chloro-acetone (VI) (16,9 g; 0,1 mole) was dissolved in glacial acetic acid (170 ml) potassium acetate (9,82 g; 0,1 mole) added and heated mildly for 10 hrs. After cooling, the separated KCl was filtered and the filtrate concentrated to small volume. Then 200 ml ether was added, dried and evaporated. The crystalline residue recrystallised from ethanol gave pure l-phenyl-3-acetoxy-acetone (VII) (15,9 g; 83%), m. p.: 64°. (Found: C 68,95; H 6,35. $C_{11}H_{12}O_3$ requires: C 68,76; H 6,22%.)

dl-1-Phenyl-2-amino-propanol-3 hydrochloride (IIb HCl). 1-Phenyl-3-acetoxy-acetone (VII) (3,84 g; 0,02 mole) was dissolved in 96 ethanol (60 ml), treated with benzylamine (2,14 g; 0,02 mole) in ethanol (40 ml) and hydrogenated over Raney-nickel catalyst (3 g) at room temperature. After the uptake of 1 mole (70 ml) hydrogen, the catalysator was filtered the coloured solution adjusted to pH 4 with ethanolic hydrochloric acid and hydrogenation continued over palladium charcoal (14% Pd; 1,2 g). On taking up the second mole hydrogen (95 min), the solution was filtered, evaporated *in vacuo*, dissolved in 1 N HCl

(20 ml), boiled for 4 hours, treated with charcoal, filtered and finally evaporated to dryness. The crystalline residue was twice recrystallised as described above to give *dl*-1-phenyl-2-amino-propanol-3-hydrochloride (IIb HCl) (1,52 g; 42%), m. p.: 137°— 140°. The latter showed no depression of m. p. on admixture with the product prepared by another method. Its liberated base melted at 87°— 88°, when purified thoroughly and gave no depression with authentic *dl*-1-phenyl-2-amino-propanol-3-al [43] (IIb).

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