Anal. Calcd. for $C_7H_{15}NO_4S$: C, 40.17; H, 7.22; N, 6.69. Found: C, 40.03; H, 7.24; N, 6.62.

Cycloheptenimine. A solution of 12.0 g. of the sulfate ester and 24 g. of sodium hydroxide in 30 ml. of water was heated in a distilling flask until the residue was nearly dry. The distillate was collected in a cooled receiver containing a little ether and sodium hydroxide pellets. The ethereal solution was separated and the aqueous solution was extracted with three 15 ml. portions of ether. The combined ether solution was dried over solid sodium hydroxide and distilled, giving 5.0 g. (78%) of colorless imine, b.p. 171–172° (uncorr.), $n_D^{20.5}$ 1.4863, $\lambda_{max}^{CCl_4}$ 3.07 μ (N—H band).

Anal. Calcd. for $C_7H_{13}N$: C, 75.61; H, 11.78; N, 12.59. Found: C, 75.33; H, 11.93; N, 12.64.

On treatment with phenyl isothiocyanate, the imine gave the *N-phenylthiocarbamyl derivative,* white needles from aqueous alcohol, m.p. 120.5°.

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37. Found: C, 68.05; H, 7.70; N, 11.50.

Hydrolysis of cycloheptenimine. A solution of 0.8 g. of the imine and 1.0 ml. of 72% perchloric acid in 8 ml. of water was refluxed for 1 hr. The solution was made strongly alkaline by the addition of sodium hydroxide and extracted with three 10 ml. portions of chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated, leaving an oily residue which upon trituration with petroleum ether (30–60°) formed a crystalline solid, m.p. 70–71°. Recrystallization from chloroform-petroleum ether raised the m.p. to 74–75°, undepressed on mixing with authentic (±)-*trans*-2-aminocycloheptanol. The identity of the hydrolysis product was further confirmed by preparation of the *N*-phenylthiocarbamyl derivative, whose m.p. and mixture m.p. were identical with the authentic material.

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Malonic Ester Synthesis of δ-Aminolevulinic Acid. The Reaction of *N*-3-Bromoacetonylphthalimide with Malonic Ester

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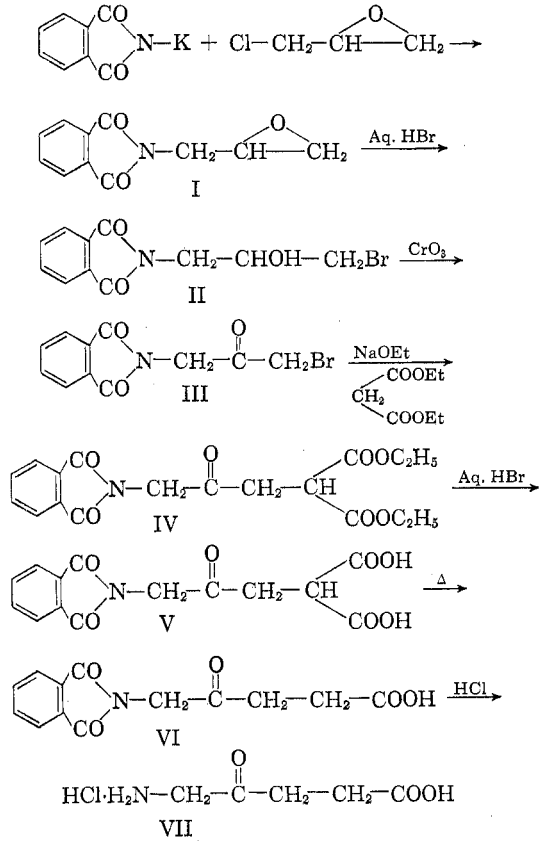
Shemin and Russell[1,2] and Neuberger and Scott[3,4] have shown δ-aminolevulinic acid (VII) to be the aliphatic precursor of the monopyrrole porphobilinogen, which is in turn the precursor of porphyrins. The biosynthesis of porphobilinogen involves an enzymatically-catalyzed Knorr condensation between two molecules of the amino ketone.[5] Of further interest is the recent demonstration by Shemin *et al.*[6] of VII as the precursor of the porphyrin-like moiety of vitamin B_{12}. Since there are relatively few organisms which do not synthesize porphyrins, it is probable that almost all living matter synthesizes VII.

A number of substituted levulinic acids have been previously prepared, but as Neuberger and Scott have indicated,[3] uniquely delta substituted derivatives were unknown until 1953 with two exceptions.[7,8] Shemin and Russell[1,2] synthesized VII by three separate routes: (1) the nitrosation of β-ketoadipic acid followed by reduction; (2) a Gabriel synthesis using δ-chlorolevulinic ester; (3) the exhaustive benzoylation of imidazolepropionic ester followed by hydrolysis.

During the course of synthesizing analogs of VII a new synthesis for this compound, outlined in the flow diagrams, was developed.



The syntheses of I, II, and III were based on those described by Weizmann and Malkova,[9] and Gabriel and Ohle.[10] The most difficult step is the coupling of III with malonic ester to form IV. Previously reported attempts at this reaction have failed to yield the desired product.[11] Thus, Haring-

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(9) M. Weizmann and S. Malkova, *Bull. soc. chim. France*, **47**, 356 (1930).

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ton and Overhoff state: "Very numerous attempts were made to condense phthalimidohalogenoacetones with ethyl sodiochloromalonate and indeed with ethyl sodiomalonate itself under various conditions, but all were in vain. The halogenoacetones reacted exothermically with the sodiomalonates with rapid elimination of the sodium halide, but normal condensation did not occur, the products consisting for the most part of highly pigmented resins."

The coupling of III with sodium diethylmalonate was studied in several solvents under various conditions and was found to yield several products. At refluxing temperature in alcohol sodium bromide was formed, but attempts to crystallize a product from alcohol, ether, and chloroform failed. A very small amount of material was crystallized from acetone, but was not studied further. When III was added as a solid to an alcoholic solution of sodium diethylmalonate at room temperature the reaction mixture crystallized spontaneously.

The material (obtained in high yield, but not the desired product) was recrystallized from 95% ethanol in which it is only slightly soluble, m.p. 278–279°. A sample was prepared for analysis by recrystallization from *N,N*-dimethylformamide by addition of water and also from alcohol-water.

The analysis suggested phthalimide (calculated for phthalimide: C: 65.30, H: 3.43, N: 9.52. Found: C: 65.24, H: 3.50, N: 9.10), but the compound differed from phthalimide in several important respects: (1) It melted 44° above phthalimide, (2) its infrared absorption spectrum was different from that of phthalimide, and (3) it was less soluble in alcohol water and *N,N*-dimethylformamide water than phthalimide. When III was allowed to react with sodium ethoxide in *N,N*-dimethylformamide, however, and the product isolated from cold dilute HCl, a considerable yield of phthalimide was obtained. Thus the desired product could not be obtained when the reaction was carried out in alcohol.

By condensing III with sodium diethylmalonate in *N,N*-dimethylformamide in dilute solution at room temperature, the desired product (IV) could be isolated by crystallization from acetone water or more readily from a large volume of petroleum ether. In the course of purification several crystalline products were obtained. The material melting at 83° was shown to be the desired product by analysis, infrared absorption spectrum and its stepwise conversion to VII. Furthermore it yielded the predicted amount of phthalic acid on acid hydrolysis (380 mg. phthalic acid recovered from hydrolysis of 840 mg. of IV, predicted: 386 mg.).

EXPERIMENTAL[12]

Ethyl-α-carbethoxy-γ-oxo-δ-phthalimidovalerate (IV). To a solution of 3.26 g. of sodium in 80 ml. dry ethanol was added 200 ml. of *N,N*-dimethylformamide and 23 ml. diethylmalonate. After allowing this to stand for 15 min. a solution of 40 g. of III in 500 ml. *N,N*-dimethylformamide was added. The temperature gradually rose to 48°. The mixture was allowed to stand overnight and then was evaporated to dryness *in vacuo*. The residue was extracted with chloroform and the NaBr filtered off. The chloroform was evaporated *in vacuo* and the residual oil was crystallized from either acetone water over a period of 4–5 days or more quickly from a large volume of petroleum ether. The 25.5 g. (49.8%) obtained was recrystallized from dilute alcohol and then water, m.p. 84°.

Anal. calcd. for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.30. Found: C, 59.79; H, 5.33.

When the same reaction was carried out with III at twice the concentration reported above, 15 g. of the material melting at 278° was obtained. This was easily separated from the desired product by dissolving the latter in alcohol or petroleum ether, since the high melting side product is only slightly soluble in alcohol and insoluble in petroleum ether.

α-carboxy-γ-oxo-δ-pthalimidovaleric acid (V). Ten g. of IV were suspended in 100 ml. of 48% HBr and allowed to stand at room temperature overnight. It was then heated on the steam bath until all the compound dissolved. The solution was allowed to cool and then evaporated to dryness *in vacuo*. The residue was recrystallized from alcohol or water to yield 7 g. (83.0%) m.p. 171–172° (with evolution of gas).

Anal. calcd. for $C_{14}H_{11}NO_7$: C, 55.08; H, 3.63; N, 4.58. Found: C, 55.38; H, 3.73; N, 4.39.

δ-Phthalimidolevulinic acid (VI). Four g. of V were heated to 170° at a pressure of 3–4 mm. Hg until the evolution of gas ceased. The glass-like residue was recrystallized from boiling water yielding 3.1 g. (90.7%) m.p. 157–158° (Neuberger and Scott[3] reported 158.5°).

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.76; H, 4.24, N, 5.36. Found: C, 60.01; H, 4.42; N, 5.47.

δ-Aminolevulinic acid hydrochloride (VII). A mixture of 4 g. of VI, 4 cc. of 95% ethanol and 40 cc. of 7*N* HCl was refluxed for 6 hr. and allowed to cool overnight. The phthalic acid was filtered off and the filtrate evaporated to dryness *in vacuo*. The slightly yellow crystals of VII weighed 2 g. (78.2%). It was recrystallized from methanol ethyl acetate m.p. 148°. It had the same ultraviolet absorption spectrum as a sample prepared by another route and also the same RF value in butanol, acetic acid, and water (.11). It was further identified by mixed melting point.

Anal. Calcd. for $C_5H_{10}NO_3Cl$: C, 35.82; H, 6.01; N, 8.35; Cl, 21.15. Found: C, 36.01; H, 6.06; N, 8.07; Cl, 20.73.

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(12) All melting points are uncorrected.

The Crystal and Molecular Structures of Overcrowded Compounds. V.[1] The Double Cyclization of Diphenethylacetic Acids

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During our work on the crystal and molecular structures of overcrowded molecules we became

(1) Part IV. F. H. Herbstein and G. M. J. Schmidt, *J. Chem. Soc.*, 3314 (1954).

(2) Weizmann Memorial Fellow 1954–55.