# Notes

A department for short papers of immediate interest.

## Chemistry of Ethylenimine. V. Cycloheptenimine or 8-Azabicyclo[5.1.0]octane[1]

PURNENDU B. TALUKDAR[2] AND PAUL E. FANTA[3]

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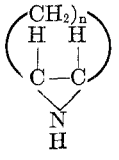
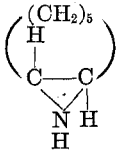
Previous papers in this series have described the preparation and hydrolysis of cyclopentenimine[4] (I) and cyclohexenimine (II).[5] These observations have now been extended to the next member of the homologous series, cycloheptenimine (III).



I. n = 3
II. n = 4
III. n = 5



IV

Cycloheptenimine was prepared from (±)-*trans*-2-aminocycloheptanol *via* the sulfate ester according to the conventional Wenker procedure. The imine is a colorless liquid which was further characterized by the preparation of a crystalline *N*-phenylthiocarbamyl derivative. Hydrolysis of the imine in aqueous perchloric acid gave (±)-*trans*-2-aminocycloheptanol. Since opening and closing of the aziridine ring occurs with inversion at the substituted carbon atom, the three- and seven-membered rings of cycloheptenimine must be fused in the *cis*-configuration.

Furthermore, in view of the unsuccessful attempt to prepare *trans*-cycloheptene oxide,[6] it is unlikely that the analogous *trans*-imine (IV) is capable of existence. However, both *cis* and *trans* imines of higher homologs in this series, analogous to the known oxides, should be possible, and this problem will be the subject of future investigation.

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(2) On study leave from the East India Pharmaceutical Works, Calcutta, India.

(3) To whom inquiries regarding this paper should be sent.

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### EXPERIMENTAL[7]

*Cycloheptene oxide.* Although this oxide has been prepared in acceptable yield by the reaction of cycloheptene with perbenzoic[8] or peracetic[8] acid, we found it more convenient to use a procedure similar to that recently described for the preparation of cyclopentene oxide.[9] A suspension of *N*-bromosuccinimide (140.6 g., 1% excess) in 310 ml. of water was stirred at 10–12° while 76.5 g. of cycloheptene was added dropwise. After 1.5 hr. of stirring at room temperature, the heavy layer of bromohydrin was separated and the aqueous solution was extracted with three 50 ml. portions of ether. The combined extract and oil was dried over anhydrous sodium sulfate and the ether was distilled, leaving crude bromohydrin in the form of a pale yellow, viscous oil.

The crude bromohydrin was added dropwise with stirring to 250 ml. of 20% aqueous sodium hydroxide at 5–7°. Stirring was continued for 2 hr. at 5–10°. The supernatant oily layer was separated and the aqueous residue was extracted with three 50 ml. portions of ether. The combined extract and oil was dried over anhydrous sodium sulfate and distilled, giving 74 g. (83% based on olefin) of colorless cycloheptene oxide, b.p. 82–84°/50 mm., $n_D^{25}$ 1.4621 (lit.[8] 83–85°/50 mm., $n_D^{25}$ 1.4615–1.4620).

(±)-*trans*-2-*Aminocycloheptanol* from the reaction of cycloheptene oxide with ammonia has been mentioned without details of the procedure.[10] A mixture of 20 g. of cycloheptene oxide and 200 ml. of 28% aqueous ammonium hydroxide was heated on a rocking steel bomb at 125° for 1 hr. The brown solution was distilled at water-aspirator pressure at first at room temperature and finally at 30–35°. The residue was taken up in chloroform, treated with Norit and concentrated to a small volume. Addition of petroleum ether and cooling overnight gave 16.2 g. (70%) of colorless amino alcohol, m.p. 74–75°. An additional crystallization from chloroform–petroleum ether (30–60°) raised the m.p. to 75–75.5° (lit.[10] 72–73°). On standing exposed to the air, the melting point of the amino alcohol rises considerably, possible due to absorption of carbon dioxide. Treatment of the amino alcohol with phenyl isothiocyanate gave the *N-phenylthiocarbamyl derivative*, white plates from aqueous ethanol, m.p. 146.5°.

*Anal.* Calcd. for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.63; N, 10.60. Found: C, 63.76; H, 7.66; N, 10.93.

(±)-*trans*-2-*Aminocycloheptyl hydrogen sulfate.* Cold 95% sulfuric acid (8.1 g.) was cautiously added to a suspension of 10.0 g. of the amino alcohol in 10 ml. of water, and the light brown solution was heated in a metal bath so that the water was slowly distilled, first at atmospheric pressure, and finally for 45 min. at a bath temperature of 135–140°/20 mm. Recrystallization of the solid residue from water with concentration of the mother liquors to get a second crop gave a total of 12.6 g. (78%) of long needles which slowly decomposed without melting at 282–284° (uncorr.). Another recrystallization from water gave silky, white needles which had the same decomposition point.

(7) Melting points are corrected except where otherwise noted. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

(8) A. C. Cope and W. N. Baxter, *J. Am. Chem. Soc.*, **76**, 279 (1954).

(9) L. Goodman, A. Benitez, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 1680 (1958).

(10) M. Godchot and M. Mousseron, *Compt. rend.*, **196**, 1680 (1933).

*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 $\mu$ (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.

DEPARTMENT OF CHEMISTRY
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO 16, ILL.

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

DONALD P. TSCHUDY AND ANNIE COLLINS

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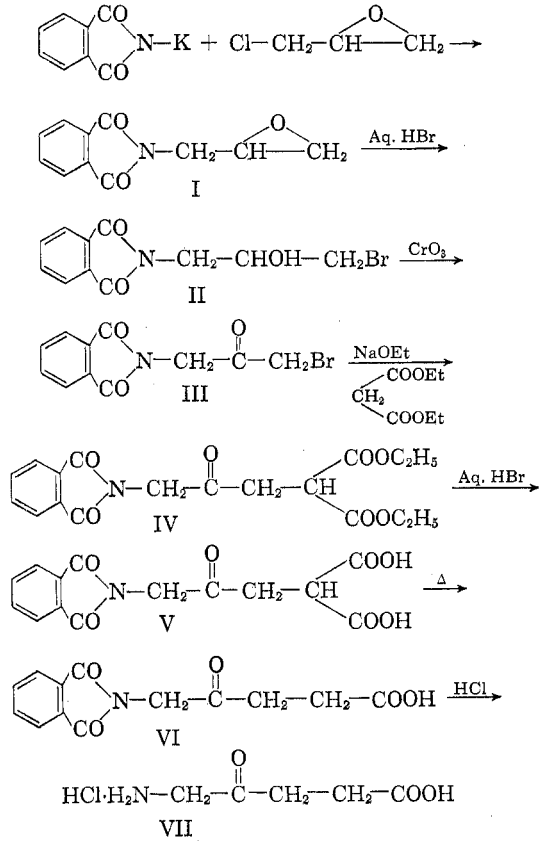
Shemin and Russell[1,2] and Neuberger and Scott[3,4] have shown δ-aminolevulinic acid (VII) to be the aliphatic precursor of the monopyrrole porphobilinogen, which is in turn the precursor of porphyrins. The biosynthesis of porphobilinogen involves an enzymatically-catalyzed Knorr condensation between 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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(3) A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1820 (1954).

(4) A. Neuberger and J. J. Scott, *Nature*, **172**, 1093 (1953).

(5) K. D. Gibson, A. Neuberger, and J. J. Scott, *Biochem. J.*, **61**, 618 (1955).

(6) D. Shemin, J. W. Corcoran, C. Rosenblum, and I. M. Miller, *Science*, **124**, 272 (1956).

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

(10) S. Gabriel and H. Ohle, *Ber.*, **50**, 822 (1917).

(11) C. R. Harington and J. Overhoff, *Biochem. J.*, **27**, 339 (1933).