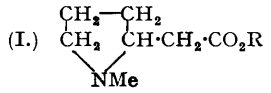
77. *A Synthesis of Ethyl* 1-*Methylpyrrolidine*-2-*acetate.*

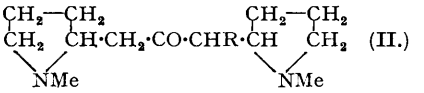
By F. E. King, J. W. Clifton, and H. T. Openshaw.

Ethyl 1-methylpyrrolidine-2-acetate (homohygrinate) (I, R = Et) has been synthesised by the condensation of *γ*-phenoxybutaldehyde with malonic acid, and conversion of the resulting *ϵ-phenoxy-*Δ^{α}*-hexenoic acid* (VIII) into *βϵ-dibromo*-n-*hexoic acid* (IX), from which homohygrinic acid was obtained by ring closure with methylamine. The product of the action of sodium on the ester (I, R = Et), when submitted to " ketonic " hydrolysis, gave a base, of which the *dipicrate* (II, R = CO_2Et) was not identical with the dipicrate of cuskhygrine.

Homohygrinic acid (I, R = H) is a degradation product of cuskhygrine (Hess and Fink, *Ber.*, 1920, **53**, 781; Winterstein and Trier, " Die Alkaloide," 2nd Ed., Berlin, 1931). Its ethyl ester (I, R = Et), synthesised by



(I.)



(II.)

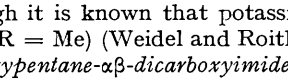
Sohl and Shriner (*J. Amer. Chem. Soc.*, 1933, **55**, 3828) *via* the pyrroleacetic ester from *N*-methylpyrrole and ethyl diazoacetate, was required for the synthesis of bis-1-methyl-2-pyrrolidylmethyl ketone (II, R = H),

which probably represents the constitution of cuskhygrine (Sohl and Shriner, *loc. cit.*). Our earlier experiments were based on a scheme requiring the dibromo-acid $Br\cdot[CH_2]_3\cdot CBr(CO_2H)\cdot CH_2\cdot CO_2H$. *Ethyl ε-phenoxypentane-αββ-tricarboxylate* (III), derived from γ-phenoxypropyl bromide and ethyl sodioethanetricarboxylate, was hydrolysed with aqueous-alcoholic potash, and decarboxylation gave *ε-phenoxypentane-αβ-dicarboxylic*

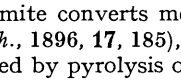
(III.) $PhO\cdot[CH_2]_3\cdot C(CO_2Et)_2\cdot CH_2\cdot CO_2Et \longrightarrow PhO\cdot[CH_2]_3\cdot CH(CO_2H)\cdot CH_2\cdot CO_2H$ (IV.)

acid (IV). Replacement of the phenoxy-group by bromine was effected with boiling hydrobromic acid, but the action of bromine on the resulting *ε-bromopentane-αβ-dicarboxylic acid* (V) failed to give any recognisable new product.

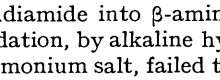
Although it is known that potassium hypobromite converts methylsuccindiamide into β-amino-*n*-butyric acid (VII, R = Me) (Weidel and Roithner, *Monatsh.*, 1896, **17**, 185), the degradation, by alkaline hypobromite, of *ε-phenoxypentane-αβ-dicarboxyimide* (VI), obtained by pyrolysis of the diammonium salt, failed to give what



(VI.)



(VII.)



(VIII.)

might have been the useful intermediate (VII, R = $PhO\cdot[CH_2]_3$). There was isolated, however, *ε-phenoxy-Δ$^{\alpha}$-hexenoic acid* (VIII), which was later synthesised in yields of 30—35% by the condensation of γ-phenoxybutaldehyde with malonic acid. The necessary aldehyde was prepared from γ-phenoxybutyronitrile by the action of stannous chloride in ethereal hydrogen chloride under special conditions (King, L'Ecuyer, and Openshaw, J., 1936, 535). The acid (VIII), dissolved in acetic acid and heated with hydrobromic acid, gave *βε-dibromo-n-hexoic acid*, $Br\cdot[CH_2]_3\cdot CHBr\cdot CH_2\cdot CO_2H$ (IX) Heating with excess of methyl-alcoholic methylamine closed the pyrrolidine ring, giving 1-methylpyrrolidine-2-acetic acid (I, R = H), which was isolated as the ethyl ester, identified by the picrate (Hess and Fink, *loc. cit.*) as ethyl homohygrinate.

Hess and Bappert (*Annalen*, 1925, **441**, 150) failed to synthesise the ketone (II, R = H) from ethyl homohygrinate by the Claisen reaction with sodium ethoxide. We treated the synthetic ester with sodium (cf. Willstätter's synthesis of tropinone; *Annalen*, 1921, **422**, 15) in toluene–ether; when the product had been heated in 50% sulphuric acid, a basic oil was obtained which gave a crystalline *dipicrate*, m. p. 155—157° (decomp.). This is not identical with cuskhygrine dipicrate, $C_{13}H_{21}ON_2,2C_6H_3O_7N_3$, m. p. 215° (Hess and Fink, *loc. cit.*), and the possibility suggested by analysis, that it is an alcoholate, $C_{25}H_{30}O_{15}N_8,EtOH$, is excluded by the thermal stability of the derivative. The analysis figures agree very satisfactorily with those required by the dipicrate of the intermediate (II, R = CO_2Et) and it is thus apparent that the action of the mineral acid had failed to hydrolyse the keto-ester.

Experimental.

Ethyl ε-Phenoxypentane-αββ-tricarboxylate (III).—A solution of sodium (15 g.) in alcohol (230 c.c.) was refluxed with ethyl ethanetricarboxylate (162 g.) and γ-phenoxypropyl bromide (142 g.) until neutral (*ca.* 5 hours), filtered, and evaporated, and the residue washed, dried, and distilled. The yield of *triethyl* ester, b. p. 203—205°/1 mm., was 65% (Found: C, 63·4; H, 7·4. $C_{20}H_{28}O_7$ requires C, 63·1; H, 7·4%).

ε-Phenoxypentane-αββ-tricarboxylic Acid.—The triethyl ester (79 g.) was refluxed in aqueous potassium hydroxide (106 g. in 90 c.c.) and alcohol (40 c.c.) for 30—40 minutes, and the liquid diluted with water (200 c.c.), concentrated to remove alcohol, and acidified with hydrochloric acid. The oily *tricarboxylic acid* (65 g.) was extracted with ether, and obtained in minute needles, m. p. 132—134° with loss of carbon dioxide, by solution in the minimum amount of ethyl acetate and precipitation with chloroform; in higher-boiling solvents, *e.g.*, water and xylene, decarboxylation occurred (Found: C, 56·3; H, 5·5. $C_{14}H_{16}O_7$ requires C, 56·7; H, 5·4%).

ε-Phenoxypentane-αβ-dicarboxylic Acid (IV).—The tribasic acid was heated for a few minutes at 150°. The residue crystallised from boiling water in colourless rectangular leaflets, m. p. 153° (Found: C, 61·8; H, 6·2. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%). A *dibromo*-derivative was prepared by addition of bromine (14—15 g.) to a chloroform solution (25 c.c.) of the acid (6 g.) containing red phosphorus (0·5 g.). After being refluxed, the solution was treated with water, and the dried chloroform layer evaporated. The residue solidified in contact with benzene; m. p. 145—146° after recrystallisation from xylene (Found: Br, 38·7. $C_{13}H_{14}O_5Br_2$ requires Br, 39·0%).

ε-Bromopentane-αβ-dicarboxylic Acid (V).—The phenoxy-acid (6 g.) was heated with hydrobromic acid (40 c.c., *d* 1·7) for 1 hour at 120—130°. The solution was diluted with water (40 c.c.) and repeatedly extracted with ether, and the dried ethereal extract evaporated. Phenol present in the residue was removed during recrystallisation from benzene–light petroleum. The *bromodicarboxylic acid* had m. p. 91—92°, and was soluble in water and common organic solvents except petroleum (Found: C, 35·4; H, 4·4; Br, 33·2. $C_7H_{11}O_4Br$ requires C, 35·2; H, 4·6; Br, 33·4%).

A solution of the acid (3 g.) in chloroform (14 c.c.) containing red phosphorus (0·3 g.) was treated with bromine (7·5 g.) and heated on a steam-bath for 3½ hours. On shaking with water and then light petroleum, a precipitate was obtained, crystalling from xylene as a colourless solid, m. p. 91—92°, or *ca.* 85° when mixed with the original acid (Found: Br, 36·1%). The same product was isolated from a bromination under similar conditions in tetrachloroethane solution. A large excess of bromine in the absence of solvent at 150° for 20 hours gave a solid crystallising from aqueous acetic acid; it contained 64·8% of bromine, but could not be purified (m. p. 122—132°).

ε-Phenoxypentane-αβ-dicarboxyimide (VI).—Ammonia was passed into a solution of the phenoxy-dicarboxylic acid in a small volume of alcohol, and the precipitated ammonium salt collected. The product, m. p. *ca.* 170°, was heated at 200°; when the evolution of gas had practically ceased, the pressure was reduced, and the temperature maintained at 190—200° for a further 20—30 minutes. The *imide* (yield, 80%) crystallised from water in leaflets, m. p. 85—86° (Found: N, 5·8. $C_{13}H_{15}O_3N$ requires N, 6·0%).

Degradation of ε-Phenoxypentane-αβ-dicarboxyimide (VI).—The imide (6 g.) was dissolved by prolonged shaking in sodium hypobromite solution prepared from bromine (4·5 g.) and ice-cold 10% aqueous sodium hydroxide (85 c.c.). The liquid was then slowly heated, maintained for 2 hours at 60°, and acidified to Congo-red with hydrochloric acid. Precipitated phenoxypentanedicarboxylic acid was removed, and the solution evaporated to dryness under diminished

pressure. From the brown uncrystallisable residue, impure ϵ-phenoxy-Δ^{α}-hexenoic acid, m. p. 77—80°, was ultimately isolated.

γ-Phenoxybutaldehyde.—Dry ether (80 c.c.) containing anhydrous stannous chloride (17 g.) was saturated at 0° with hydrogen chloride, and to the clear liquid (see King, L'Ecuyer, and Openshaw, *loc. cit.*) γ-phenoxybutyronitrile (10 g.) (Marvel and Tanenbaum, *J. Amer. Chem. Soc.*, 1922, **44**, 2645) was added. Two layers formed, but as no solid separated, the mixture was refluxed for 6 hours, cooled to 0°, and resaturated with hydrogen chloride. The stannichloride dissolved when shaken with ether (25 c.c.) and water (80 c.c.) containing a trace of quinol. From the ethereal layer, γ-phenoxybutaldehyde (8 g.) was isolated as a nearly colourless oil that slowly became turbid from polymerisation. The *semicarbazone*, a microcrystalline powder from benzene, had m. p. 118° (Found: C, 59·9; H, 6·8. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·8%).

ϵ-Phenoxy-Δ^{α}-hexenoic Acid (VIII).—To a cold solution of malonic acid (17 g.) and freshly prepared phenoxybutaldehyde (8 g.) in pyridine (25 c.c.), piperidine (1·5 c.c.) was cautiously added, and the solution kept at room temperature for 3—4 hours. Following 6 hours' heating on a steam-bath, the liquid was acidified with 5% sulphuric acid, and the sticky precipitate washed and shaken with aqueous sodium carbonate. The filtered alkaline solution on acidification gave *ϵ-phenoxy-Δ^{α}-hexenoic acid* which, extracted (Soxhlet) with and crystallised from light petroleum, gave plates, m. p. 86° (Found: C, 69·5; H, 6·7. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%) (yield, 30—35%).

βϵ-Dibromo-n-hexoic Acid (IX).—A solution of the phenoxyhexenoic acid (11 g.) in acetic acid (50 c.c.) and hydrobromic acid (100 c.c., *d* 1·7) containing red phosphorus (0·5 g.) was refluxed in carbon dioxide for 2½ hours and poured into water. The precipitated reddish oil was extracted with chloroform, dried, and distilled, giving phenol and a principal fraction (11·2 g., 76%), b. p. 150—155°/1 mm., redistillisation of which gave a colourless oil, b. p. 154°/1 mm., consisting largely of the *dibromo-acid* (Found: C, 27·2; H, 3·6; Br, 57·3. $C_6H_{10}O_2Br_2$ requires C, 26·3; H, 3·6; Br, 58·4%).

Ethyl 1-Methylpyrrolidine-2-acetate (I, R = Et).—A solution of the dibromohexoic acid (11·2 g.) and anhydrous methylamine (10 g.) in methyl alcohol (16 c.c.) was heated in three sealed tubes at 100° for 4 hours and at 110° for ½ hour. The semi-solid product remaining after evaporation of the golden-yellow liquid under diminished pressure was dried overnight in a vacuum desiccator and refluxed for 5 hours with ethyl-alcoholic hydrogen chloride (50 g. of 15%). The alcohol was evaporated, water (10 c.c.) added, the solution basified with cold aqueous sodium hydroxide, and ethyl 1-methylpyrrolidine-2-acetate (2·25 g.; 33%) quickly extracted with ether and distilled (Found: C, 62·6; H, 10·0; N, 8·4. Calc. for $C_9H_{17}O_2N$: C, 63·2; N, 9·9; N, 8·2%). Cold saturated alcoholic picric acid gave a bright yellow picrate with the recorded m. p. 113° (Hess and Fink, *loc. cit.*) (Found: N, 14·2. Calc.: N, 14·0%).

The pyrrolidine ester (1·8 g.), dissolved in anhydrous ether (3 c.c.), was added to pulverised sodium (0·25 g.) in toluene (3 c.c.); the sodium dissolved in 5 minutes. Ice-water was added and the aqueous solution and the washings of the toluene–ether layer were acidified (4·5 g. of sulphuric acid in 5 c.c. of water), heated on a steam-bath for 1 hour, cooled, and basified with solid sodium hydroxide. The precipitated yellow oil was extracted with ether and treated with alcoholic picric acid, and the gummy solid dissolved in boiling alcohol–acetone. Resinous solid which separated on cooling was removed, and the solution concentrated. The resulting precipitate crystallised from alcohol–acetone in clusters of bright yellow tablets, m. p. 155—157° (decomp.) [Found: C, 44·6, 44·8; H, 5·0, 5·0; N, 15·4. *Ethyl β-keto-αγ-di-(1-methyl-2-pyrrolidyl)butyrate dipicrate*, $C_{18}H_{28}O_3N_2,2C_6H_3O_7N_3$, requires C, 44·5; H, 4·5; N, 14·9%). $C_{13}H_{24}ON_2,2C_6H_3O_7N_3,C_2H_5OH$ requires C, 44·5; H, 5·0; N, 15·4%, but no loss in weight could be detected on heating to 120° in a vacuum].

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