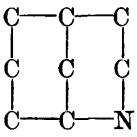
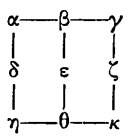
CCCXXI.—3-*Hydroxy*cyclo*hexylacetolactone.*

By ROBERT ROBINSON and AHMAD ZAKI.

ACCORDING to Gulland and Robinson (J., 1923, **123**, 980; *Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10), whose suggestions have been amply justified by the important and outstanding experiments of Schöpf (*Annalen*, 1927, **452**, 211), the bases of the morphine group contain the heterocyclic system (I) associated with other rings.

(I.)



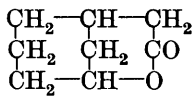


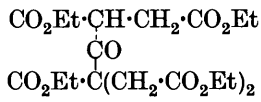
(II.) $\zeta = O$
(III.) $\varepsilon = N$
(IV.) $\beta = \theta = N$
(V.) $\delta = \zeta = N$
(VI.) $\alpha = \gamma = \eta = \kappa = N$

An examination of the literature shows that substances of this type have not been obtained although the similar systems indicated by II, III, IV, V, and VI (where each letter represents a carbon atom except when otherwise specified) are found among synthesised compounds. It is proposed to attempt the synthesis of simple bases of the type (I) in order to examine the degree of stability of the ring structure. Progress in this direction has been made and is reported at this stage because one of us is unable to continue the work.

There is little doubt that the desired base could be obtained from the *lactone* (VII), named in the title, and we have obtained this substance by the reduction of *m*-hydroxyphenylacetic acid with hydrogen in the presence of platinum-black. The yield, however, is poor, the main product being hexahydrophenylacetic acid. It seemed that a better method of preparation might be through

(VII.)





(VIII.)

3-keto*cyclo*hexylacetic acid, which might be derived by applying the Dieckmann reaction to the ester of methanediacetic-γ-butyric acid, $CH(CH_2 \cdot CO_2H)_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CO_2H$. The latter we hoped to obtain from the tribasic keto-acid which should be the normal product of hydrolysis of the ester (VIII). This has been prepared, but the scheme broke down owing to the wasteful nature of the operations necessary for the introduction of acetic residues into ethyl acetonedicarboxylate.

EXPERIMENTAL.

m-*Hydroxyphenylacetic Acid.*—Anhydro-α-benzamido-*m*-methoxycinnamic acid (35 g.) was hydrolysed as described by Pschorr (*Annalen*, 1912, **391**, 44), but the resulting alkaline solution was

then acidified by the passage of sulphur dioxide, which precipitated the benzoic acid (compare Buck and Perkin, J., 1924, **125**, 1680). After filtration, concentrated hydrochloric acid was added and the solution boiled to expel sulphur dioxide; on cooling, *m*-methoxyphenylpyruvic acid (14 g.) separated (m. p. 154—155° after crystallisation from alcohol). This acid (8·4 g.) was dissolved in 10% sodium hydroxide (70 c.c.), and 3% hydrogen peroxide (50 c.c.) added. After being kept over-night in the cold, the solution was acidified, and *m*-methoxyphenylacetic acid (6 g., m. p. 66—67° after one crystallisation from water) was isolated by means of ether. *m*-Hydroxyphenylacetic acid has been previously obtained by Salkowski (*Ber.*, 1884, **17**, 507) from *m*-nitrophenylacetonitrile by a series of reactions; we have prepared it by demethylation of its methyl ether: *m*-methoxyphenylacetic acid was boiled with 8 times its weight of freshly distilled hydriodic acid (*d* 1·7) for 2 hours. The solution was cooled and diluted with water, free iodine removed by sulphur dioxide, and the acid isolated by ether as a brown oil which gradually crystallised. The product was purified by one crystallisation from benzene, dissolution in aqueous sodium carbonate, successive extraction of the alkaline solution with carbon disulphide and ether, recovery by means of ether, and a final crystallisation from benzene. The acid had the m. p. (129°) and other properties attributed to it by Salkowski (*loc. cit.*).

Catalytic Reduction of m-*Hydroxyphenylacetic Acid.*—A solution of *m*-hydroxyphenylacetic acid (4·5 g.) in acetic acid (20 c.c.) was vigorously stirred with hydrogen in presence of platinum-black (0·7 g.), prepared by Willstätter's method (*Ber.*, 1912, **45**, 1472). After a little time the flask was evacuated and the mixture stirred with air for 10 minutes; on re-evacuation and admission of hydrogen the rate of absorption was found to have been almost quadrupled. In about 12 hours 2330 c.c. of hydrogen had been absorbed. The filtered solution was steam-distilled until about 2000 c.c. of distillate had been collected; the liquid remaining in the flask was then thoroughly extracted with ether, and after removal of the solvent the residue was twice distilled under diminished pressure. The product appeared to be homogeneous, but owing to the small amount available we do not record the b. p. under diminished pressure; under the ordinary pressure, it has b. p. 240—243°, determined by Siwoloboff's method (*Ber.*, 1886, **19**, 795) (Found: C, 69·0; H, 8·5. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%). This colourless oil is clearly 3-*hydroxy*cyclo*hexylacetolactone*, for it exhibits the behaviour of a lactone: it is immiscible with water, and on the addition of a drop of sodium hydroxide and a trace of phenolphthalein a red coloration is obtained, which soon disappears,

further quantities of sodium hydroxide being similarly slowly neutralised until the whole of the substance has been decomposed. On acidifying and heating the solution, the lactone was regenerated. The distillate from the steam-distillation contained an acid which was isolated by means of ether and distilled. The fraction, b. p. 243—246°, crystallised in the course of 2 days in large, feather-like aggregates, m. p. 30—31° (Found: C, 67·6; H, 10·0. Calc. for $C_8H_{14}O_2$: C, 67·6; H, 9·8%). From the origin, m. p., analysis, and other properties, there can be no doubt that this substance is identical with hexahydrophenylacetic acid (Wallach, *Annalen*, 1907, **353**, 296). It constituted the main product of the reduction.

Ethyl βδ-*Dicarbethoxy*-γ-*ketopimelate*,

$$CO_2Et{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}CO_2Et.$$

—An alcoholic solution of sodium ethoxide (from 6·9 g. of sodium) was added during 1½ hours to a mixture of ethyl acetonedicarboxylate (30·3 g.) and ethyl bromoacetate (50 g.), heated on the steam-bath. The mixture was then heated under reflux till neutral, the alcohol distilled, and the product isolated from the residue by means of ether. Thorough drying was found to be essential. The oil was fractionated under 1 mm. pressure, but this process entailed large losses through decomposition. Finally, a homogeneous fraction, b. p. 168—170°/1 mm., was collected (10 g.) (Found: C, 54·8; H, 7·0. $C_{17}H_{26}O_9$ requires C, 54·6; H, 6·9%). Analysis does not determine whether the acetonedicarboxylic ester has been converted into a mono-, di-, tri-, or tetra-substituted derivative, so the ester was hydrolysed by boiling dilute sulphuric acid: acetonediacetic acid, m. p. 142—143° (Volhard, *Annalen*, 1889, **253**, 212) was readily isolated (Found: C, 48·1; H, 6·0. Calc. for $C_7H_{10}O_5$: C, 48·3; H, 5·7%).

Ethyl αββ′-*Tricarbethoxy*isobutyrylsuccinate (VIII).—This substance was obtained from molecular proportions of the foregoing ester (24·7 g.), ethyl bromoacetate, and sodium ethoxide in alcoholic solution. The yield of pure product, b. p. 189—191°/1 mm., was 17 g. (Found: C, 54·8; H, 7·0. $C_{21}H_{32}O_{11}$ requires C, 54·8; H, 6·9%). This would correspond to a 56% yield of the monosubstituted derivative, or a 47% yield of the disubstituted derivative. In view of the amount of recovered material of lower and higher b. p. (10 g. containing at least 2 g. of ethyl bromoacetate) and of the fact that the maximum theoretical yield of disubstituted derivative was 50%, a 47% yield of disubstituted derivative is impossible. The polybasic acid obtained by hydrolysing this ester could not be crystallised.

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