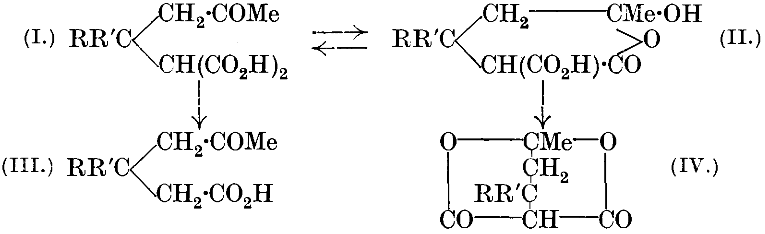
CCL.—*Studies in Keto-lactol Tautomerism. Part III. Influence of Bulky Substituents on the Tautomerism of α-Carboxy-γ-acetyl-β-methyl-β-ethyl-butyric and -ββ-diethylbutyric Acids.*

By MUHAMMAD QUDRAT-I-KHUDA.

IN previous parts of this series (this vol., pp. 201, 713) the effects of *gem*-dimethyl groups and *cyclo*hexane and *cyclo*pentane ring systems on the tautomerism of the δ-ketodibasic acids of type (I) $\rightleftharpoons$ (II) were studied, and it was shown that *cyclo*hexane-1-acetone-1-malonic acid (I; RR′ = $C_5H_{10}>$) was readily converted *via* (II) into the corresponding dilactone (IV) on being heated in certain high-boiling organic solvents. On the other hand, when the substituents were either *gem*-dimethyl groups or part of the *cyclo*pentane ring, the conversion of the acids into the dilactone took place only to a small extent in solution, but more readily in the presence of some dehydrating agents or concentrated hydrochloric acid. When the acids were heated alone in the liquid state, an equilibrium mixture was formed consisting of both the forms (I) and (II), which yielded respectively the dilactone (IV) and the keto-monobasic acid (III) by decomposition.



It was thought desirable to examine the rôle played by bulky substituents on the tautomerism of these acids, and in the present communication the effects of methylethyl and *gem*-diethyl groups on the tautomerism of the corresponding acids (I; RR′ = Me,Et) and (I; RR′ = Et_2) are described.

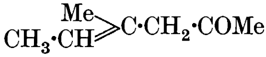
The present series of investigations indicates, in accordance with the views of Thorpe and his collaborators (Dickens, Kon, and Thorpe, J., 1922, **121**, 1496; Deshapande and Thorpe, *ibid.*, p. 1430; Ingold, Sako, and Thorpe, *ibid.*, p. 1181; Singh and Thorpe, J., 1923, **123**, 113), that qualitatively the effect of the groups examined on the carbon tetrahedral angle is in the order : *cyclo*hexane >*gem*-diethyl >methylethyl>*gem*-dimethyl.

The position of *gem*-diethyl with respect to methylethyl is shown by the fact that the amount of dilactone obtained by the pyrogenic decomposition of *α-carboxy-γ-acetyl-ββ-diethylbutyric acid* (I; RR′ = Et_2) represents 45% of the dibasic acid, whilst that from *α-carboxy-γ-acetyl-β-methyl-β-ethylbutyric acid* (I; RR′ = Me,Et) represents only 32%. Both these acids undergo conversion into the dilactone when heated in benzene solution for some time, the change in the case of the diethyl compound being more marked. It should also be mentioned that the *cyclo*pentane and *gem*-dimethyl homologues partly undergo the same conversion on prolonged heating in solution.

For the preparation of α-carboxy-γ-acetyl-β-methyl-β-ethylbutyric acid (I; RR′ = Me,Et), methyl β-methyl-Δ^{α}-butenyl ketone (V) was required. By the action of zinc methyl iodide on the acid chloride of either β-methyl-Δ^{α}- or -Δ^{β}-pentenoic acid, a ketone was obtained which appeared to be a mixture of the unsaturated ketones (V) and (VI), giving a eutectic mixture of semicarbazones, m. p. 86°, which could not be separated into the two components (compare Abbott, Kon, and Satchell, J., 1928, 2514).

(V.)

$\genfrac{}{}{0pt}{}{Me}{Et}{>}C{:}CH\cdot COMe$

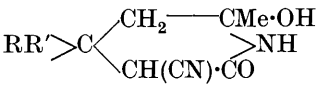


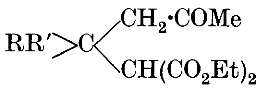
$\genfrac{}{}{0pt}{}{Me}{CH_3\cdot CH}{>}C\cdot CH_2\cdot COMe$

(VI.)

When the mixture of ketones was condensed with sodiocyanoacetamide, 6-*hydroxy*-2-*keto*-3-*cyano*-4 : 6-*dimethyl*-4-*ethylpiperidine* (VII; RR′ = Me,Et) was obtained, whilst a similar condensation with methyl β-ethyl-Δ^{α}-butenyl ketone or its Δ^{β}-isomeride gave 6-*hydroxy*-2-*keto*-3-*cyano*-6-*methyl*-4 : 4-*diethylpiperidine* (VII; RR′ = Et_2) in fairly good yield. These piperidine derivatives on alkaline hydrolysis give α-carboxy-γ-acetyl-β-methyl-β-ethylbutyric and -ββ-diethylbutyric acids, respectively, and these acids on esterification give the normal *keto-esters* (VIII). The ethoxy-ester (IX)

(VII.)

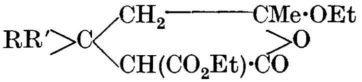


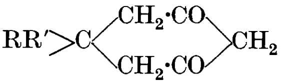


(VIII.)

could not be obtained, but in the case of the diethyl compound it was necessary to esterify the acid through the *silver* salt, for otherwise the ordinary processes of esterification give an impure mixture of the normal ester together with a small quantity of the dilactone. The esters give well-defined *semicarbazones* in conformity with their keto-configuration. Although the acids also give *semicarbazones*, they react in their lactol form in the presence of dehydrating agents or concentrated hydrochloric acid.

(IX.)



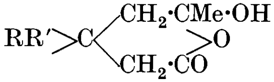


(X.)

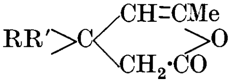
These acids on being heated alone a few degrees above their melting points decompose into the respective *dilactones* and the corresponding keto-monobasic *acids* (III), the *ethyl* esters of which were synthesised for the purpose of comparison from the acid esters of the respective glutaric acids through the Blaise–Maire reaction. Ethyl γ-acetyl-β-methyl-β-ethylbutyrate (δ-keto-β-methyl-β-ethyl-*n*-hexoate) is converted into 5-*methyl*-5-*ethyldihydroresorcinol* (X; RR′ = Me,Et) when heated with alcoholic sodium ethoxide solution, whilst the higher homologue is similarly converted into Kon and Linstead's diethyldihydroresorcinol (X; RR′ = Et_2) (J., 1925, **127**, 818).

These ethyl esters, on hydrolysis, yield the corresponding keto-monobasic acids, which have been compared through their semicarbazones with the acids obtained by the pyrogenic decomposition of the corresponding dibasic acids. The monocarboxylic acids also exist in their lactol form (XI), for when treated with acetyl chloride they yield the corresponding unsaturated *lactones* (XII), apparently through the loss of a molecule of water.

(XI.)



$RR'{>}C{<}\begin{matrix}CH_2\cdot CMe\cdot OH\\ CH_2\cdot CO\end{matrix}{>}O$

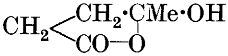


$RR'{>}C{<}\begin{matrix}CH{=}CMe\\ CH_2\cdot CO\end{matrix}{>}O$

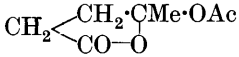
(XII.)

Ordinary lævulic acid reacts in its lactol modification (XIII), giving the acetyl derivative (XIV) by treatment with acetic anhydride (Bredt, *Annalen*, 1890, **256**, 314), and a series of substituted lævulic acids is now under investigation in order to determine the extent of this tautomeric change and its dependence on structure.

(XIII.)



$CH_2{<}\begin{matrix}CH_2\cdot CMe\cdot OH\\ CO{-}O\end{matrix}$



$CH_2{<}\begin{matrix}CH_2\cdot CMe\cdot OAc\\ CO{-}O\end{matrix}$

(XIV.)

EXPERIMENTAL.

Methylethyl Series.

Synthesis of the Mixture of the αβ- *and* βγ-*Unsaturated Isomerides of Methyl* β-*Methyl*-Δ^{α}-*butenyl Ketone.*—The same ketone was prepared by the action of zinc methyl iodide on the acid chloride of both β-methyl-Δ^{α}- and -Δ^{β}-pentenoic acid, the yield being about 40% in each case. When treated with semicarbazide acetate in the usual way, the ketone readily yields a high-melting solid (a semicarbazide semicarbazone ?) together with a *semicarbazone*, which is very soluble in methyl alcohol, but crystallises from benzene–light petroleum; m. p. 86° (Found : C, 57·0; H, 7·9. $C_8H_{15}ON_3$ requires C, 56·8; H, 8·8%). Only once, a second *semicarbazone* was obtained from the ketone prepared from the acid chloride of β-methyl-Δ^{α}-pentenoic acid; it crystallised from dilute methyl alcohol in shining plates, m. p. 155° (Found : C, 56·5; H, 9·0%). The ketone regenerated from the semicarbazone of m. p. 86° has b. p. 40°/10 mm.,

$d_{4^\circ}^{18\cdot3^\circ}$ 0·85631, $n_D^{18\cdot3^\circ}$ 1·44010, whence $[R_L]_D$ 34·48 (calc., 34·07) (Found : C, 74·9; H, 11·0. Calc. for $C_7H_{12}O$: C, 75·0; H, 10·7%). Addition of iodine to an *M*/300-solution of this ketone in chloroform was carried out by the method of Linstead and May (J., 1927, 2565); the value obtained in 10 minutes was 55%, whence the ketone consists of a mixture of the αβ- and βγ- unsaturated isomerides.

6-*Hydroxy*-2-*keto*-3-*cyano*-4 : 6-*dimethyl*-4-*ethylpiperidine* (VII; RR′ = Me,Et).—Methyl β-methyl-Δ^β-butenyl ketone (25·2 g.) was heated with a suspension of sodiocyanoacetamide (from 18·9 g. of cyanoacetamide in 200 c.c. of hot alcohol, and 5·2 g. of sodium in 70 c.c. of alcohol), according to the general method already described (this vol., p. 716). The condensation *product* (27 g.) was recrystallised from hot water (Found : C, 61·0; H, 8·4. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2%). It is a beautifully crystalline solid, m. p. 240°, soluble in hot water, alcohol, and acetic acid, but insoluble in benzene, chloroform, and ether.

α-*Carboxy*-γ-*acetyl*-β-*methyl*-β-*ethylbutyric Acid*.—The piperidine compound (25 g.) was hydrolysed with aqueous caustic potash (25 g. in 110 c.c.) by heating for 16 hours. The *acid*, isolated in the usual way, slowly solidified in a vacuum desiccator (25 g.); it crystallises from chloroform–ethyl bromide and melts at 89° (Found : C, 55·6; H, 7·8; *M*, by titration, 216. $C_{10}H_{16}O_5$ requires C, 55·6; H, 7·4%; *M*, 216). The acid is soluble in most organic solvents, but not in ethyl bromide or light petroleum. When heated in a benzene solution for about an hour, 18% of it was transformed into the dilactone described below. It gives a *semicarbazone*, which crystallises from hot water and melts at 166° (Found : C, 48·5; H, 7·1. $C_{11}H_{19}O_5N_3$ requires C, 48·4; H, 7·0%). When esterified with alcoholic hydrogen chloride the acid gives only the open-chain *diethyl* ester, b. p. 154°/10 mm., $d_{4^\circ}^{16\cdot2^\circ}$ 1·0414, $n_D^{16\cdot2^\circ}$ 1·44873, whence $[R_L]_D$ 70·02 (calc., 70·17) (Found : C, 61·6; H, 9·1. $C_{14}H_{24}O_5$ requires C, 61·8; H, 8·8%); this gives a *semicarbazone*, which crystallises from benzene–petroleum in clusters of needles, m. p. 89° (Found : C, 54·4; H, 8·4. $C_{15}H_{27}O_5N_3$ requires C, 54·7; H, 8·2%).

Behaviour of α-*Carboxy*-γ-*acetyl*-β-*methyl*-β-*ethylbutyric Acid on Heating : Formation of the Dilactone* (as IV) *and of* γ-*Acetyl*-β-*methyl*-β-*ethylbutyric Acid*.—The acid (5·47 g.) was heated at 130—140° for 5 hours and the melt was cooled, dissolved in benzene, and extracted with dilute sodium carbonate solution. When the benzene layer was dried and the solvent removed, 1·78 g. of the solid *dilactone* were obtained (representing 33% of the total acid); this crystallised from dilute alcohol and had m. p. 82° (Found : C, 60·5; H, 7·3. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). When hydrolysed with dilute caustic alkalis, the dilactone gives α-carboxy-γ-acetyl-β-methyl-β-ethylbutyric acid as the sole product, and when heated alone it decomposes slowly at 220° into the unsaturated lactone described below.

The sodium carbonate extract on acidification gave 2·68 g. of an oily acid, identified as γ-acetyl-β-methyl-β-ethylbutyric acid (see below) (Found, for the *silver* salt : Ag, 38·7. $C_9H_{15}O_3Ag$ requires Ag, 38·7%). The acid readily gave a *semicarbazone*, which crystallised from hot water or dilute alcohol; m. p. 152° (Found : C, 52·3; H, 8·3. $C_{10}H_{19}O_3N_3$ requires C, 52·4; H, 8·3%), unaltered in admixture with the semicarbazone of the synthetic keto-acid described below.

Synthesis of Ethyl γ-Acetyl-β-methyl-β-ethylbutyrate.—β-Methyl-β-ethylglutaric acid, obtained by Singh and Thorpe's method (*loc. cit.*), readily yields an anhydride on heating with acetic anhydride; its anhydride (80 g.), when boiled with alcohol (120 c.c.) on the steam-bath for 3—4 hours, was converted into ethyl hydrogen β-methyl-β-ethylglutarate, which was isolated in the usual way and obtained, on removal of the solvent, as a somewhat thick oil (Found for the *silver* salt : Ag, 35·1. $C_{10}H_{17}O_4Ag$ requires Ag, 35·0%). The acid ester (40 g.) was mixed with thionyl chloride (30 c.c.) and heated in a water-bath at 50—60° for 1½ hours, the excess of thionyl chloride was removed under diminished pressure, and the residue thus obtained added to a well-cooled benzene solution of zinc methyl iodide (compare this vol., p. 208). The required *ester*, isolated from the benzene solution, boils at 120—126°/18 mm., and when regenerated from the semicarbazone it has b. p. 112°/10 mm., $d_4^{17.4°}$ 0·967526, $n_D^{17.4°}$ 1·43899, whence $[R_L]_D$ 54·37 (calc., 54·56) (Found : C, 66·0; H, 10·0. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%); the *semicarbazone*, crystallised from methyl alcohol, had m. p. 94° (Found: C, 55·8; H, 9·1. $C_{12}H_{23}O_3N_3$ requires C, 56·0; H, 8·9%). The substituted butyric ester (4·5 g.), when heated with sodium (0·5 g.) in absolute alcohol (30 c.c.) for 4 hours on the steam-bath, gave 5-*methyl*-5-*ethyldihydroresorcinol* (2·4 g.), which gives an orange colour with alcoholic ferric chloride, dissolves in dilute alkalis, and crystallises from benzene–petroleum in prismatic needles, m. p. 106° (Found : C, 69·9; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%).

Preparation of γ-Acetyl-β-methyl-β-ethylbutyric Acid.—The above ester (30 g.) was heated on the steam-bath for 5 hours with caustic potash (30 g.) in water (30 c.c.) and enough alcohol to give a uniform solution. The alcohol was then removed, and the residue was diluted with water, freed from unchanged ester by extraction with ether, and then acidified. The precipitated oil was dissolved in ether, the solution dried, and the solvent removed; the thick syrupy residue obtained was distilled under low pressure. *γ-Acetyl-β-*

methyl-β-*ethylbutyric acid* boils at 150°/10 mm., and has $d_{4^\circ}^{18\cdot1^\circ}$ 1·0425, $n_D^{18\cdot1^\circ}$ 1·45773, whence $[R_L]_D$ 45·0 (calc., 45·31) (Found : C, 62·8; H, 9·5; *M*, by titration, 172. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%; *M*, 172); the semicarbazone from this synthetic acid melted at 152° (Found : C, 52·5; H, 8·5%).

Action of Acetyl Chloride on γ-Acetyl-β-methyl-β-ethylbutyric Acid.—The acid (7 g.) was treated with excess of acetyl chloride (10 c.c.) and heated on the steam-bath under reflux until the evolution of hydrogen chloride had ceased (1½ hours); the excess of acetyl chloride was decomposed with water, and the oil that separated was extracted with ether, washed with sodium carbonate solution, dried, and distilled in a vacuum. The *lactone* of δ-hydroxy-β-methyl-β-ethyl-Δ^{γ}-hexenoic acid (as XII) has a characteristic odour and has b. p. 90°/10 mm., $d_{4^\circ}^{18\cdot4^\circ}$ 0·991443, $n_D^{18\cdot4^\circ}$ 1·4622, whence $[R_L]_D$ 42·72 (calc., 42·75) (Found : C, 70·1; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%).

Diethyl Series.

Methyl β-ethyl-Δ^{α}-butenyl ketone was prepared by Kon and Linstead's method (*loc. cit.*). From both the αβ- and the βγ-isomeride, the same condensation product was obtained, but as the former gave a better yield, it was mainly used in the following process; after two distillations, it had b. p. 62°/15 mm., $d_{4^\circ}^{18\cdot1^\circ}$ 0·86224, $n_D^{18\cdot1^\circ}$ 1·44773.

6-*Hydroxy*-2-*keto*-3-*cyano*-6-*methyl*-4 : 4-*diethylpiperidine* (VII; RR′ = Et_2).—Methyl β-ethyl-Δ^{α}-butenyl ketone (38 g.) was condensed with cyanoacetamide (25 g.) in 288 c.c. of alcohol containing sodium (7 g.); the condensation *product* (yield 48 g.) crystallised from dilute acetic acid, and had m. p. 251° (Found : C, 61·9; H, 8·6. $C_{11}H_{18}O_2N_2$ requires C, 62·3; H, 8·6%). It is soluble in hot water, alcohol, and acetic acid, but practically insoluble in cold water, benzene, and ether. When heated with concentrated hydrochloric acid, it gave the dilactone described below as the only product.

Preparation of α-Carboxy-γ-acetyl-ββ-diethylbutyric Acid.—The above condensation product (48 g.) was hydrolysed with potassium hydroxide (48 g.) in 210 c.c. of water by heating for 40 hours on a sand-bath (shorter periods give low yields). The *acid* isolated in the usual way solidified in a vacuum desiccator (47 g.); when crystallised from chloroform–ethyl bromide it melts at 97° (Found : C, 57·4; H, 7·8; *M*, by titration, 230. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·8%; *M*, 230); the *semicarbazone*, m. p. 158° (Found : C, 50·2; H, 7·6. $C_{12}H_{21}O_5N_3$ requires C, 50·2; H, 7·3%), crystallises from hot water. The acid is converted into the dilactone to the extent of 68% on being heated for about an hour in a benzene solution.

The *ethyl* ester of the above acid (VIII; RR′ = Et_2), prepared by heating the dry disilver salt with excess of ethyl iodide in absolute-alcoholic solution, and isolated in the usual way, boils at 167°/12 mm., and has $d_{4^\circ}^{17\cdot6^\circ}$ 1·0405, $n_D^{17\cdot6^\circ}$ 1·45553, whence $[R_L]_D$ 74·79 (calc., 74·79) (Found : C, 62·9; H, 9·1. $C_{15}H_{26}O_5$ requires C, 62·9; H, 9·1%); its *semicarbazone*, crystallised from benzene–light petroleum (b. p. 60—80°), melts at 88° (Found : C, 55·8; H, 8·8. $C_{16}H_{29}O_5N_3$ requires C, 55·9; H, 8·4%).

Behaviour of α-Carboxy-γ-acetyl-ββ-diethylbutyric Acid on Heating : Preparation of the Dilactone (as IV) *and of γ-Acetyl-ββ-diethylbutyric Acid.*—The keto-dibasic acid (7 g.) was heated and the product worked up under exactly the same conditions as for the lower homologue (p. 1916); the *dilactone* obtained (2·9 g., representing 45% of the total acid) crystallises from dilute alcohol and melts at 113° (Found : C, 62·1; H, 7·8. $C_{11}H_{16}O_4$ requires C, 62·2; H, 7·6%).

The alkaline extract on acidification gave 3·05 g. of γ-acetyl-ββ-diethylbutyric acid as an oil; the *semicarbazone*, which crystallised from methyl alcohol, melts at 155° (Found : C, 54·2; H, 8·8. $C_{11}H_{21}O_3N_3$ requires C, 54·3; H, 8·6%), and is identical with that obtained from the synthetic acid described below.

Synthesis of Ethyl γ-Acetyl-ββ-diethylbutyrate.—ββ-Diethylglutaric acid, obtained by the method described by Deshapande and Thorpe (*loc. cit.*), gave an anhydride when heated with acetic anhydride, and when boiled with twice the required quantity of absolute alcohol, this anhydride was converted into the acid ester, obtained as a thick syrupy liquid (Found, for the *silver* salt : Ag, 33·4. $C_{11}H_{19}O_4Ag$ requires Ag, 33·4%). The ethyl hydrogen ββ-diethylglutarate (35 g.) was heated with a slight excess of thionyl chloride (15 c.c.) at 60—65° in a water-bath until evolution of hydrogen chloride had ceased, excess of thionyl chloride was removed under reduced pressure at the same temperature, and the residue without further purification was added to a cold benzene solution of zinc methyl iodide. The *ethyl γ-acetyl-ββ-diethylbutyrate* (27 g.) obtained in the usual way boils at 120—126°/12 mm., and when regenerated from the semicarbazone has b. p. 125°/11 mm., $d_{4^\circ}^{18\cdot8^\circ}$ 0·966424, $n_D^{18\cdot8^\circ}$ 1·44392, whence $[R_L]_D$ 58·81 (calc., 59·28) (Found : C, 67·2; H, 10·3. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%). The *semicarbazone*, crystallised from dilute methyl alcohol, melts at 93° (Found : C, 57·2; H, 9·5. $C_{13}H_{25}O_3N_3$ requires C, 57·5; H, 9·2%).

γ-Acetyl-ββ-diethylbutyric Acid.—The crude ester, when hydrolysed by alcoholic caustic potash, gave a thick syrupy liquid consisting of γ-acetyl-ββ-diethylbutyric acid and a small quantity of ββ-diethylglutaric acid; separation was effected by treating the mixture with hot petroleum (b. p. 60—80°) in which the latter is insoluble. The petroleum was distilled from the solution and the residue fractionated under diminished pressure; the acid was thus obtained as a colourless syrupy liquid, b.p. 158°/10 mm., $d_{4°}^{14·2°}$ 1·04214, $n_{D}^{14·2°}$ 1·46639, whence $[R_L]_D$ 49·47 (calc. for open-chain form, 49·93) (Found : C, 64·2; H, 9·8; *M*, by titration, 186·5. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·8%; *M*, 186); the semicarbazone (Found : C, 54·1; H, 8·7%) melts at 155° (compare above).

*Action of Acetyl Chloride on γ-Acetyl-*ββ*-diethylbutyric Acid.*—The syrupy acid (5 g.) and acetyl chloride (10 c.c.) were allowed to react as in the case of the lower homologue (p. 1918), and the product was worked up as before. The *lactone* of δ-hydroxy-ββ-diethyl-Δ^{γ}-hexenoic acid boils at 106°/10 mm., and has $d_{4°}^{17·2°}$ 0·996021, $n_{D}^{17·2°}$ 1·46867, whence $[R_L]_D$ 47·19 (calc., 47·36) (Found : C, 71·4; H, 9·8. $C_{10}H_{17}O_2$ requires C, 71·4; H, 9·5%).

In conclusion, the author desires to record his grateful thanks to Professor J. F. Thorpe, C.B.E., F.R.S., for his kind interest in this investigation, and to the Government of Bengal for a foreign scholarship and a grant towards the purchase of chemicals.

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