# *Experiments with* 5 : 6-*Dihydro*-4-*hydroxy*-6-*phenyl*-2-*pyrone. Part II.* The Basic Hydrolysis of an α-Bromo- and an αα-Dibromo*-β-*keto*-δ-*lactone.*

By Evans B. Reid and Joel R. Siegel.

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Oxidation of 5 : 6-dihydro-4-hydroxy-6-phenyl-2-pyrone with lead tetra-acetate yielded no clearly defined products. Bromination in a basic medium furnished the 3-bromo-derivative, which exists in two forms. Under hydrolytic conditions the bromo-pyrone appears to undergo a series of consecutive rearrangements, yielding 2-phenylethyltartronic acid; a mechanism is advanced to account for this transformation. The hydroxy-pyrone also forms a crystalline 3 : 3-dibromo-derivative. Attempts to replace the bromine atoms with oxygen were without success, as were efforts to oxidise the parent pyrone directly to the 3 : 4-dioxo-derivative. Evidence is advanced to show that the latter is too unstable for isolation. On reduction, or on hydrolysis, one bromine atom is reduced with the formation of the monobromo-pyrone.

The experiments described in this paper were initiated with a view to developing, on model compounds, procedures that might be applicable to the ultimate synthesis of auxin-a from auxin-b (Kögl, Erxleben, Michaelis, and Visser, *Z. physiol. Chem.*, 1935, **235**, 181). Since sodium borohydride had proved an effective reagent for the reduction of both 1 : 2-dicarbonyl and 1-acetoxy-1-carbonyl compounds (Reid and Siegel, preceding paper), efforts were first directed toward the hydroxylation and/or the acetoxylation of 5 : 6-dihydro-4-hydroxy-6-phenyl-2-pyrone (I) which is the phenyl analogue of auxin-b in lactone form (Henbest and Jones, *J.*, 1950, 3628; Reid and Ruby, Part I*).

Lead tetra-acetate acetoxylates the methylene group of ethyl acetoacetate (Dimroth and Schweizer, *Ber.*, 1923, **56**, 1380). It readily oxidised the hydroxy-pyrone (I), but the products obtained under various experimental conditions were orange gums that contained lead and slowly hardened in the atmosphere. When they were freed from lead, yellow amorphous inhomogeneous powders remained. These were readily oxidised by Tollens's reagent, and this, together with the absence of a typical colour reaction with sodium nitrite (Wolff, *Annalen*, 1898, **291**, 244; Reid and Ruby, *loc. cit.*) and the formation of a dark precipitate with ferric chloride, indicated that lead tetra-acetate had probably functioned, at least in part, as a dehydrogenating agent (cf. Haworth *et al.*, *J.*, 1935, 635, 643; 1936, 352, 1000; Newman, *J. Amer. Chem. Soc.*, 1940, **62**, 1683) to produce a mixture containing the pyrone (II). Analyses, however, were too erratic to substantiate this conclusion.

In view of the sensitivity of the hydroxy-pyrone to oxidising agents our attention turned to substitution methods, and for these, use of the 3-iodo-pyrone seemed the most desirable. Unfortunately, attempts to iodinate the hydroxy-pyrone were unsuccessful: in hypoiodite solution cleavage occurred, leading to iodoform amongst other products, probably as follows:

$$\text{(I)} \longrightarrow \text{Ph·CH:CH·CO·CH}_2\text{·CO}_2^- \longrightarrow \text{Ph·CH:CH·COMe} \longrightarrow \text{CHI}_3$$

(cf. Henbest and Jones, and Reid and Ruby, *locc. cit.*). On the other hand, in aqueous-methanolic sodium hydroxide the hydroxy-pyrone smoothly furnished the crystalline, enolic, monobromide (III; R = Br). Proof that the bromine atom was attached to the α-carbon atom was afforded by further bromination to a *non-enolic* dibromopyrone (see below).

The bromo-pyrone, after repeated recrystallisations from aqueous ethanol, had m. p. 133—134° (decomp.), but exhibited a peculiarity of the hydroxy-pyrone (I) in that its melting point was dependent upon the nature of the solvent used for crystallisation (Reid and Ruby, *loc. cit.*). Thus, after several recrystallisations from benzene, the melting point was 154—155° (decomp.). The compound reverted to the lower-melting form on recrystallisation

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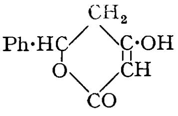
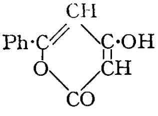
* Part I, *J. Amer. Chem. Soc.*, 1951, **73**, 1054.

from hydroxylic solvents. This behaviour is not shown by the enol-ethers or the non-enolic dibromo-derivative of (I). It appeared at first, therefore, that this characteristic was to be attributed to differences in some function, such as hydrogen bonding, for which the enolic hydroxyl group was responsible. However, the infra-red absorption spectra of both forms of the bromo-pyrone were virtually identical and revealed no evidence of hydrogen bonding. The two forms thus appear to be dimorphic modifications, as with the parent hydroxy-pyrone (Reid and Ruby, *loc. cit.*).

Several attempts were made to convert the bromo-pyrone into the acyloin (III; R = OH). With silver oxide suspended in aqueous alcohol no replacement of bromine occurred, the insoluble silver enolate apparently being formed. In hot benzene silver acetate reacted readily, but the product was an intractable gum that appeared to be a decomposition product.

Extended treatment in hot aqueous base removed the bromine atom, furnishing a homogeneous acidic material whose analysis accommodated the structure of the acyloin, but with the incorporation of 1·5 mols. of water. The absence of benzaldehyde amongst the products of oxidation of this substance by potassium permanganate lent credence to the acyloin structure, which was also in harmony with the observation that ceric ion was quickly reduced by the product and by lactic acid. However, titration with the Karl Fischer reagent revealed the empirical formula to be $C_{11}H_{12}O_5,\frac{1}{2}H_2O$, and the facts that the compound failed to respond to 2 : 4-dinitrophenylhydrazine, and in titration showed the presence of two carboxyl groups, definitely eliminated the acyloin possibility.


(I)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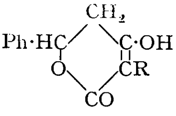
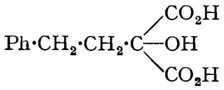
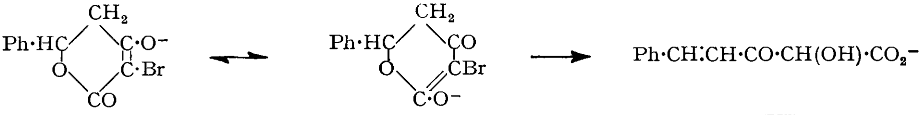

(III)


$Ph{\cdot}CH_2{\cdot}CH_2{\cdot}C(OH)(CO_2H)_2$

(IV)

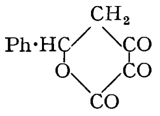
The presence of a hydroxyl group adjacent to carboxyl was implied by the above-mentioned oxidation by ceric ion, and was substantiated by the observation that in fuming sulphuric acid carbon monoxide was evolved vigorously. That these units were part of a malonic acid grouping was established by decarboxylation, thermally or on acid catalysis, to α-hydroxy-γ-phenylbutyric acid. 3-Bromo-5 : 6-dihydro-4-hydroxy-6-phenyl-2-pyrone (III; R = Br) is thus transformed by basic hydrolysis into a product which, on the basis of the above evidence, can only be 2-phenylethyltartronic acid (IV). In basic solution the bromo-pyrone will exist completely in the anionic form (V $\leftrightarrow$ V*a*); hydrolysis of the bromine atom will therefore not occur without prior or concomitant ring opening (cf. ring scission of the parent pyrone type; Jones and Whiting, *J.*, 1949, 1419, 1423; Reid and Ruby, *loc. cit.*) resulting in the unsaturated acyloin (VI); this, by a base-catalysed Lobry de Bruyn–van Eckenstein rearrangement, would be expected to equilibrate with the isomeric acyloin (VII), in which $C_{(3)}$ is flanked by two electrophilic groupings so that consequent loss of proton facilitates isomerisation to (VIII); the αβ-diketone (VIII), by the usual benzilic acid rearrangement (cf. Davis *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 3304) would furnish 2-phenylethyltartronic acid (IV), the product isolated.

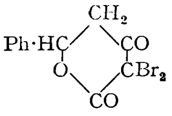

(V) (V*a*) (VI)

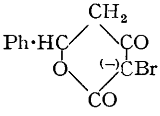
It should be pointed out that the above mechanism is not entirely without experimental support, for in refluxing base benzylidenelactic acid is known to isomerise to α-oxo-γ-phenylbutyric acid (Petkov, *Annalen*, 1898, **299**, 26).

As a possible method for circumventing the above difficulty, and at the same time providing a direct route from the hydroxy-pyrone (I) to the desired 3 : 4-dioxo-pyrone (IX), oxidations with selenium dioxide were explored. This reagent, which oxidises the methylene hydrogen atoms of ethyl acetoacetate (Müller, *Ber.*, 1933, **66**, 1668), readily attacked the pyrone with formation of the expected intense orange colour. Less than half of the theoretical amount of metallic selenium could be recovered, however, and the product, a deep orange-coloured solid was obviously a complex of selenium, as attested by its colour reaction with thiourea and hydrochloric acid (Lange, " Handbook of Chemistry," Handbook Publ., Inc., 6th Edn., 1946, Sandusky, Ohio, p. 1137), and by the inability of sulphur dioxide to effect separation (Wattkins and Clark, *Chem. Reviews*, 1945, **36**, 235). In attempts to obtain a pure organic material by reaction with *o*-phenylenediamine, the product, whilst free from selenium, was an amorphous oxygen-sensitive substance that rapidly decomposed on attempted recrystallisation. Although this product appeared to be derived from an α-diketone, this approach had to be abandoned in favour of less direct ones.

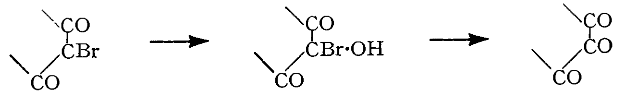
$$\begin{tikzcd}
\text{(VII)}\ \mathrm{Ph\cdot CH{:}CH\cdot CH(OH)\cdot CO\cdot CO_2^-} \arrow[r, "-\mathrm{H}^+"] & \mathrm{Ph\cdot CH{:}CH\cdot \overset{-}{C}(OH)\cdot CO\cdot CO_2^-} \arrow[d, shift left] \\
\text{(VIII)}\ \mathrm{Ph\cdot CH_2\cdot CH_2\cdot CO\cdot CO\cdot CO_2^-} \arrow[r, "+\mathrm{H}^+"] & \mathrm{Ph\cdot \overset{+}{C}H\cdot CH{:}C(OH)\cdot CO\cdot CO_2^-} \arrow[u, shift left]
\end{tikzcd}$$


(IX)


(X)

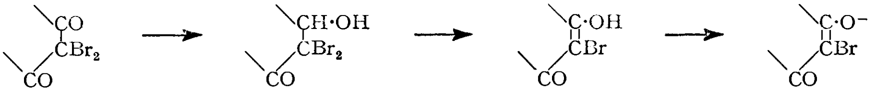

(XI)

Further bromination of the hydroxy-pyrone (I) in a basic medium gave a crystalline dibromo-pyrone (X). The yield was greatly improved by isolation of the intermediate monobromo-pyrone (III; R = Br). The dibromide was non-enolic to ferric chloride solution, and failed to develop colour in the sodium nitrite test, thus affording clear proof of the absence, on the part of both the monobromide and the dibromide, of the α → γ rearrangement typical of α-bromoacetoacetic esters (Conrad and Schmidt, *Ber.*, 1896, **29**, 1042; Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655). Since tests with boiling silver nitrate solutions revealed ready and quantitative removal of *one* bromine atom, experiments were directed toward the formation of the 3 : 4-dioxo-pyrone by metathetical reactions. Use of *either* silver acetate (compare the action of this reagent on ethyl dibromomalonate to yield ethyl mesoxalate and acetyl bromide; Anschutz and Parlato, *Ber.*, 1892, **25**, 3614) *or* silver oxide, gave the expected orange colour characteristic of 1 : 2 diketones, but, as with selenium dioxide oxidation, the products were orange gums that appeared to have undergone partial degradation, yielding cinnamic aldehyde amongst other products. With *o*-phenylenediamine brown powders were obtained that decomposed in air or on attempted recrystallisation. Similar results were obtained upon treating the dibromo-pyrone itself with *o*-phenylenediamine. The conclusion appeared inescapable that whilst the dioxo-pyrone was probably formed as a primary product it was too unstable to permit isolation (cf. the instability of 3-oxotetronic acid; Michael and Jung, *Ber.*, 1934, **67**, 1660). It thus appeared doubtful whether aqueous hydrolysis, (XII) → (XIV), could be realised, particularly since reductive hydrolysis of the dibromo-grouping would be expected to be a competing reaction. Nevertheless, hydrolysis of the dibromo-pyrone was attempted, first in basic solution, and later in aqueous acetone. The exclusive product, however, was the monobromo-pyrone (III; R = Br), and the reaction gave evidence of formation of hypobromite ion. It has been shown by Altschul and Bartlett (*J. Org. Chem.*, 1940, **5**, 623) that " positivity " of bromine in α-bromo-ketones is dependent on structure and, whilst in some cases negligibly slight, is never entirely absent. On this view, the above


(XII) (XIII) (XIV)

example must be considered a classical one, for the substance is so sensitive to reductive hydrolysis that it is difficult to recrystallise it from hydroxylic solvents without the formation of some monobromo-pyrone. The driving force in this reaction is presumably due to the easy formation of the ion (XI), which, is the electronic equivalent of (V) and (V*a*).

Resonance stabilisation of the bromo-anion, in the sense indicated by (V) and (V*a*), would be eliminated if reduction of the β-oxo-group to the alcohol could be accomplished. The specificity involved in such a reduction would obviously require the use of sodium borohydride (Reid and Siegel, preceding paper). This reagent, however, failed to reduce either the bromo-pyrone (III; R = Br) or the parent pyrone (I). It readily attacked the dibromo-pyrone (X), but yielded the monobromo-derivative exclusively. In this case it



(XV) (XVI) (XVII) (XVIII)

is probable that the reaction was not a hydrolytic reduction, but a true reduction of the carbonyl group, and that the monobromo-pyrone resulted from dehydrohalogenation, as indicated in (XV) ⟶ (XVIII).

## EXPERIMENTAL

*Oxidation with Lead Tetra-acetate.*—The α-form of the hydroxy-pyrone (Reid and Ruby, *loc. cit.*) (5·89 g., 0·0309 mole), in absolute ethyl acetate (400 ml.) was stirred under nitrogen while lead tetra-acetate (13·9 g., 0·031 mole) was added slowly, the temperature being kept below 38°. Ethylene glycol was then added to destroy the excess of tetra-acetate (starch-iodide test), while the mixture was stirred for an additional 15 min. The precipitated lead salts were collected and dissolved in pyridine, and the lead was removed with hydrogen sulphide. The residue was diluted with an equal volume of water, cooled in an ice-bath, and rapidly acidified to pH 2 with dilute hydrochloric acid, causing precipitation of a yellow solid. Evaporation of the ethyl acetate filtrate (above) yielded an orange syrup. This was taken up in pyridine and treated as above, forming the yellow solid in larger amounts (combined yield, 2·50 g.). The product was an intractable mixture: recrystallised from benzene it slowly decomposed at 116—120°; recrystallised from benzene–ligroin it decomposed at 125—135°. The mixed m. p. with original α-pyrone was 105°. The product gave positive tests for the carbonyl group and formed a dark precipitate with ferric chloride solution. With sodium nitrite no colour developed, but positive tests were obtained with both Tollens's and Fehling's solutions. The average of several analyses failed to prove the presence of 4-hydroxy-6-phenyl-2-pyrone (Found: C, 68·4; H, 4·8. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%).

3-*Bromo*-5 : 6-*dihydro*-4-*hydroxy*-6-*phenyl*-2-*pyrone*.—The hydroxy-pyrone (4·74 g., 0·0249 mole) was dissolved in 24·9 ml. of N-sodium hydroxide containing 6 ml. of methanol, cooled below 10°, and rapidly stirred while a solution of bromine (3·98 g., 0·0249 mole) in 29·8 ml. of methanol containing 10 ml. of water was added dropwise. Ice-water (6 ml.) was then added, and the precipitate was collected, washed with ice-water (40 ml.), and air-dried, to give the crude product (5·3 g., 79·3%). On recrystallisation from alcohol–water (2 : 1) colourless needles of the β-*form* of 3-*bromo*-5 : 6-*dihydro*-4-*hydroxy*-6-*phenyl*-2-*pyrone*, m. p. 133—134° (decomp.), were obtained (Found: C, 49·0; H, 3·4; Br, 29·7. $C_{11}H_9O_3Br$ requires C, 49·1; H, 3·4; Br, 29·7%).

Several recrystallisations from benzene ultimately raised the m. p. to 154—155° (decomp.) (α-*form*) (Found: C, 49·3; H, 3·3; Br, 29·5%).

The α-form was reconverted into the β-form by recrystallisations from aqueous ethanol. Both forms gave intense purple colours with ferric chloride, and with sodium nitrite solution deep pink colours developed in a few minutes. On warming of the bromo-pyrone with a suspension of silver oxide in aqueous ethanol a precipitate containing silver and bromine slowly formed. Ready reaction occurred with silver acetate in hot benzene but gave only gums.

2-*Phenylethyltartronic Acid*.—The bromo-pyrone (5·86 g., 0·02 mole), dissolved in N-sodium hydroxide (185 ml.), was refluxed for 5 hr., cooled, and extracted with ether. Acidification (hydrochloric acid), extraction with ether (five times), drying ($Na_2SO_4$), evaporation, and recrystallisation from chloroform or water gave colourless 2-*phenylethyltartronic acid*, m. p. 135—137° (decomp.), containing ½ mol. of water of crystallisation (Karl Fischer determination)

(Found: C, 56·9; H, 6·1; $H_2O$, 3·9. $C_{11}H_{12}O_5,\frac{1}{2}H_2O$ requires C, 56·6; H, 5·6; $H_2O$, 3·9%) (2·08 g., 47·2%). The compound decolorised ceric nitrate solution, and evolved carbon monoxide vigorously in warm oleum. It was inert to 2 : 4-dinitrophenylhydrazine, and on titration proved to be dibasic.

*α-Hydroxy-γ-phenylbutyric Acid*.—2-Phenylethyltartronic acid (0·330 g.) was heated under reflux with 9% hydrochloric acid (12 ml.) for 7 hr. and then kept at room temperature for 10 hr. Colourless needles were precipitated. These were washed with ice-water and dried (m. p. 103—105°; 34%) (Found: C, 66·5; H, 6·5. $C_{10}H_{12}O_3$ requires C, 66·65; H, 6·7%). The same product, *α-hydroxy-γ-phenylbutyric acid*, was obtained by heating the tartronic acid at 150° for 25 min. and recrystallising the residue from benzene.

*β-Phenylpropaldehyde*.—α-Hydroxy-γ-phenylbutyric acid (0·09 g., 0·005 mole), lead peroxide (0·12 g., 0·005 mole), phosphoric acid (0·049 g.), acetic acid (3 g.), and water (5 ml.) were refluxed for 2 hr., and the cooled mixture was filtered with suction. Treatment of the filtrate with 2 : 4-dinitrophenylhydrazine gave β-phenylpropaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 148—150°.

*Oxidation of* 5 : 6-*Dihydro*-4-*hydroxy*-6-*phenyl*-2-*pyrone*.—The pyrone (1 g., 0·0053 mole) in hot anhydrous benzene was treated with selenium dioxide (0·59 g., 0·0053 mole). The solution became yellow and then orange. After 3·5 hours' heating, the mixture was filtered, yielding about 40% of the calculated amount of metallic selenium. Evaporation furnished 0·9 g. of an orange selenium-containing solid, soluble in benzene, dioxan, or acetone. Heating this with *o*-phenylenediamine in acetic acid gave a deep red solution which, when poured into water, yielded an orange solid (100 mg.). This gave the purple colour with sulphuric acid characteristic of quinoxaline derivatives (Hickinbottom, " Reactions of Organic Compounds," Longmans Green and Co., London, 1st Edn., 1936, p. 294) and contained no selenium. It rapidly decomposed in air and on attempted crystallisation.

3 : 3-*Dibromo*-5 : 6-*dihydro*-4-*oxo*-6-*phenyl*-2-*pyrone*.—This substance was prepared in one step by treatment of the pyrone in basic solution with two equivs. of bromine, but was best prepared by bromination of the monobromopyrone. The monobromopyrone (6·6 g., 0·025 mole), dissolved in N-sodium hydroxide (24·5 ml.), was cooled below 10° and stirred vigorously while bromine (3·93 g., 0·025 mole), in water–ethanol (20 + 20 ml.), was added dropwise. The precipitated dibromo-pyrone (7·8 g., 85·5%) was washed with water and dried *thoroughly* before recrystallisation. A 72·5% yield of 3 : 3-*dibromo*-5 : 6-*dihydro*-4-*oxo*-6-*phenyl*-2-*pyrone* was obtained as colourless needles, m. p. 114—116°, on recrystallisation from chloroform–hexane (1 : 1) (Found: C, 38·0; H, 2·2; Br, 45·7. $C_{11}H_8O_3Br_2$ requires C, 38·0; H, 2·3; Br, 45·9%).

In *fresh* alcoholic solution the product gave no colour with sodium nitrite solution (Wolff, *loc. cit.*; Reid and Ruby, *loc. cit.*), or dilute ferric chloride. When the dibromo-pyrone (0·2807 g.) in ethanol (50 ml.) containing water (10 ml.) and silver nitrate (0·4 g.) was boiled for 1 hr., 27·8% of the bromine was removed (Calc.: 22·9% for *one* atom).

*Reactions with Silver Oxide and Silver Acetate*.—The dibromo-pyrone (0·5 g., 0·0014 mole) in anhydrous benzene was heated with silver oxide (0·33 g., 0·0014 mole) until a deep orange colour developed (5·5 hr.). Filtration removed silver bromide and some unchanged oxide, and gave a clear orange solution, which on evaporation yielded an orange gum. Treatment with water failed to lessen the colour and gave no noticeable reaction, although a faint odour of cinnamon was apparent. With *o*-phenylenediamine in acetic acid a tan-coloured solid was formed that blackened in air and on attempted recrystallisation.

With silver acetate (0·24 g., 0·0014 mole) the dibromo-pyrone (0·5 g., 0·0014 mole) in hot anhydrous benzene reacted to yield silver bromide and a deep orange-coloured solution. After 3 hours' heating the product was an orange gum.

*Hydrolysis of the Dibromo-pyrone*.—(a) *With aqueous base*. The dibromo-pyrone (0·5 g., 0·0014 mole) was heated for 10 min. on the steam-bath with N-sodium hydroxide (20 ml.). Tests for hypobromite ion (starch–iodide) were positive. On dilution and acidification at 0° a small amount of the enolic monobromo-pyrone was precipitated.

(b) *With aqueous acetone*. The dibromo-pyrone (337 mg.) was dissolved in warm acetone–water (30 : 20), and the solution set aside for a day. After removal of the solvent *in vacuo*, the solid residue was crystallised from water–ethanol, yielding the monobromo-pyrone (75 mg., 28·8%), m. p. and mixed m. p. with authentic low-melting form, 132·5—133·5° (decomp.). After four recrystallisations from benzene, the m. p. and mixed m. p. with authentic high-melting form were 153—154° (decomp.).

*Reduction of the Dibromo-pyrone*.—The dibromo-pyrone (300 mg., 0·0086 mole), dissolved in absolute methanol (10 ml.), was added dropwise to sodium borohydride (0·3 g., 0·003 mole) in absolute methanol (10 ml.). The reaction was very vigorous. Decomposition of the excess of borohydride with dilute hydrochloric acid precipitated the monobromo-pyrone. After recrystallisation from ethanol–water, the m. p. and mixed m. p. with authentic low-melting form were 132·5—134·5° (decomp.). After several recrystallisations from anhydrous benzene, the m. p. and mixed m. p. with authentic high-melting form were 152·5—153·5° (decomp.). The yield was nearly quantitative.

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THE JOHNS HOPKINS UNIVERSITY,
BALTIMORE 18, MARYLAND, U.S.A.

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