

577. *Studies of Compounds Related to Natural Perfumes. Part II.*
The Application of the Diels–Alder Reaction to the Synthesis of
 β -cycloCitral Analogues.

By J. C. LUNT and FRANZ SONDHEIMER.

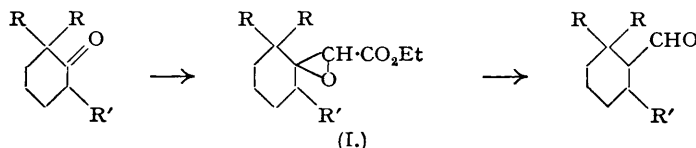
The aldehyde (II), obtained by the Diels–Alder reaction between 1-methylbutadiene and crotonaldehyde, is hydrogenated to the saturated aldehyde (III). This is brominated to (IV), which on dehydrobromination gives the unsaturated aldehyde (V), a lower homologue of β -cyclocitral. The Diels–Alder reaction between 1:1:3-trimethylbutadiene and crotonaldehyde is shown to give exclusively 2:2:4:6-tetramethylcyclohex-3-enealdehyde (VIII). This is converted by the same reaction sequence into 4-methyl- β -cyclocitral (XIII).

Most of the practicable authenticated methods for the synthesis of β -cyclocitral and β -ionone, and related six-membered ring analogues (particularly of the irone type), involve the cyclisation of an acyclic compound at some stage. Recently, two new methods for the synthesis of β -ionone analogues have been developed (Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1949, 737), based on the corresponding cyclohexanones and cyclohexanealdehydes, severally. The first method, involving the ethynylcyclohexenes as intermediates, has since been extended (Heilbron, Jones, Toogood, and Weedon, *J.*, 1949, 2208) and has also been used for the preparation of cyclopentenyl and cycloheptenyl analogues of β -ionone (Heilbron, Jones, Toogood, and Weedon, *J.*, 1949, 1827). The present communication

describes the progress made in developing the second procedure, which involves the bromination, followed by dehydrobromination, of saturated *cyclohexanealdehydes*.

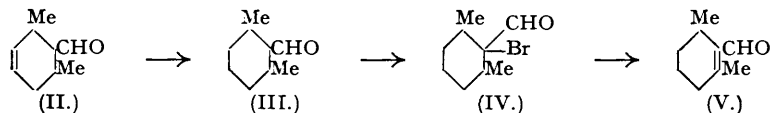
In principle there are several methods available for preparing alkyl-substituted *cyclohexanealdehydes*. Among these may be mentioned: (a) the Grignard reaction of the corresponding bromides with ethyl orthoformate, followed by hydrolysis of the acetal (cf. Smith *et al.*, *J. Org. Chem.*, 1941, **6**, 437, 489), (b) addition of hydrogen and carbon monoxide to *cyclohexenes* (cf. Adkins and Krsek, *J. Amer. Chem. Soc.*, 1949, **71**, 3051), (c) the Darzens reaction of the corresponding *cyclohexanones* with ethyl chloroacetate, followed by hydrolysis and decarboxylation of the glycidic esters (cf. Newman and Magerlein, "Organic Reactions," John Wiley, New York, 1949, Vol. 5, 413), and (d) the Diels–Alder reaction between substituted butadienes and $\alpha\beta$ -unsaturated aldehydes, followed by hydrogenation of the *cyclohexenealdehydes* formed. The last two of these methods have been investigated.

A convenient procedure for carrying out the Darzens reaction between carbonyl compounds and ethyl chloroacetate, using sodium in xylene as condensing agent, has been described in the patent literature (B.P. 372,013; G.P. 591,452, 602,816; U.S.P. 1,899,340). This has the advantage over the more usual techniques (sodium alkoxides, sodamide, or sodium in ether) in that no solid material separates during the reaction, and a completely clear solution is obtained. In this way *cyclohexanone* was smoothly converted into the glycidic ester (I; R = R' = H),



which has already been transformed into *cyclohexanealdehyde* (Darzens and Lefébure, *Compt. rend.*, 1906, **142**, 714; Newman and Magerlein, *J. Amer. Chem. Soc.*, 1947, **69**, 469). When this reaction was carried out with 2 : 2-dimethyl*cyclohexanone*, only a 15% yield of crude undistilled ester (I; R = Me, R' = H) was obtained, most of the ketone being recoverable. With 2 : 2 : 6-trimethyl*cyclohexanone* the steric hindrance of the methyl groups was sufficient completely to prevent reaction, the starting material being recovered quantitatively. This method is therefore not applicable to the preparation of the required alkylated *cyclohexanealdehydes*. After this work had been completed, a paper by Horning, Horning, and Platt (*J. Amer. Chem. Soc.*, 1949, **71**, 1771) described the Darzens reaction with 2 : 2 : 3-trimethyl- and 2 : 2 : 3 : 6-tetramethyl-*cyclohexanones*, in which the results agreed closely with those of the present communication.

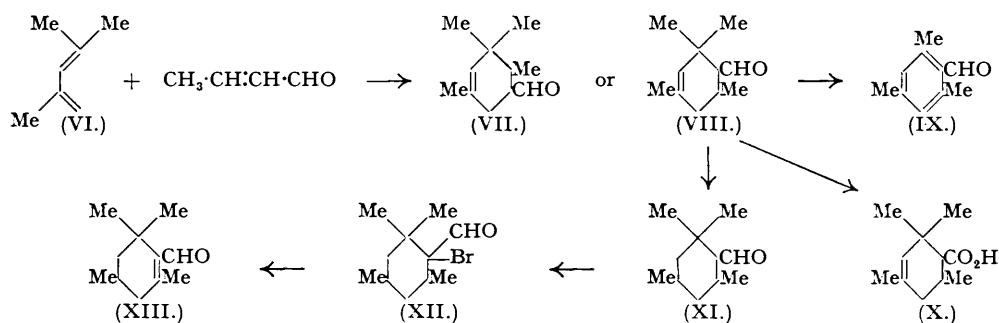
Attention was then turned to method (d). The Diels–Alder adduct of crotonaldehyde and 1-methylbutadiene (piperylene) has been shown to have structure (II) (Holmes, Alcock, Demianow, Robinson, Rooney, and Sunberg, *Canadian J. Res.*, 1948, **26**, B, 248). We have found the adduct to be homogeneous, both by careful fractionation and by the fact that only one 2 : 4-dinitrophenylhydrazone was formed. When (II) was hydrogenated with a palladium–



calcium carbonate catalyst, 1 mole of hydrogen was absorbed and 2 : 6-dimethyl*cyclohexanealdehyde* (III) (2 : 4-dinitrophenylhydrazone) was isolated in 68% yield. Bromine in chloroform (Barbier, *Helv. Chim. Acta*, 1940, **23**, 793; Heilbron, Jones, Richardson, and Sondheimer, *loc. cit.*) gave a 52% yield of the unstable bromo-aldehyde (IV). When the latter was boiled with diethylaniline for 2 minutes, hydrogen bromide was eliminated, and impure 2 : 6-dimethyl*cyclohex-1-enealdehyde* (V) (2 : 4-dinitrophenylhydrazone) was obtained. It was converted into the semicarbazone (54% yield based on the bromo-aldehyde), from which the pure aldehyde was regenerated.

The same sequence of reactions was performed on the aldehyde (VIII), the product of the Diels–Alder reaction between crotonaldehyde and 1 : 1 : 3-trimethylbutadiene (2 : 4-dimethylpenta-1 : 3-diene) (VI). This reaction might give rise to two aldehydes (VII) and (VIII), and it has previously been carried out by Diels and Alder (*Annalen*, 1929, **470**, 62), and described in the patent literature (Naef *et Cie.*, F.P. 672,025; Swiss P. 136,907); however, no yields were

given, nor was the product characterised. The German authors, without evidence, assumed structure (VIII) for the product, but the patents considered both aldehydes to be formed, the major product also being assigned structure (VIII) on the basis of the hydrolysis rate of the corresponding ester. It was found that under the conditions used by Diels and Alder (heating at 180° for 7 hours) only a 20% yield of adduct was obtained. The reaction was run under a variety of conditions, and the best yield (42%) of adduct was produced on heating the components at 155° for 40 hours. The product appeared homogeneous and it gave essentially only one 2 : 4-dinitrophenylhydrazone (see Experimental). It was dehydrogenated by sulphur (cf. Holmes *et al.*, *loc. cit.*) to 2 : 4 : 6-trimethylbenzaldehyde (IX) characterised as the 2 : 4-dinitrophenylhydrazone. It is concluded that the aldehyde (VIII) is the only product of the Diels-Alder reaction. Similarly, Jitkow and Bogert (*J. Amer. Chem. Soc.*, 1941, **63**, 1979) found that the reaction between 1 : 1 : 3-trimethylbutadiene and acraldehyde gave essentially only the adduct corresponding to structure (VIII). On the other hand, Naves and Ardizio (*Helv. Chim. Acta*, 1948, **31**, 2252) concluded that the reaction between 1 : 1 : 2-trimethylbutadiene and crotonaldehyde gave a mixture of the two possible adducts, the major product possessing the structure corresponding to (VII). On oxidation with silver oxide, the adduct (VIII) gave the crystalline acid (X), m. p. 85—87°, which is probably identical with the acid (m. p. 88.5—89°) obtained by Diels and Alder (*loc. cit.*) from 1 : 1 : 3-trimethylbutadiene and crotonic acid.



On catalytic hydrogenation, rather more than 1 mole of hydrogen was absorbed and 2 : 2 : 4 : 6-tetramethylcyclohexanealdehyde (XI) (2 : 4-dinitrophenylhydrazone) could be isolated. Bromination with bromine in chloroform gave the bromo-aldehyde (XII) (50% yield), which on treatment with diethylaniline eliminated hydrogen bromide to give crude 2 : 2 : 4 : 6-tetramethylcyclohex-6-enealdehyde (4-methyl- β -cyclocitral) (XIII). The latter was isolated as its semicarbazone (31% yield based on the bromo-aldehyde), and was also characterised by its 2 : 4-dinitrophenylhydrazone.

The light-absorption data of the final compounds described in this paper are recorded in the table and are seen to be in good agreement with those of β -cyclocitral and its derivatives.

Compound. (V)	Aldehyde.		Semicarbazone.		2 : 4-Dinitrophenyl- hydrazone.*	
	$\lambda_{\text{max.}}$, A.	$\epsilon_{\text{max.}}$	$\lambda_{\text{max.}}$, A.	$\epsilon_{\text{max.}}$	$\lambda_{\text{max.}}$, A.	$\epsilon_{\text{max.}}$
(V)	2470	12,400	2730	20,100	3910	29,900
(XIII)	—	—	2770	19,100	3840	26,600
2 : 2 : 6-Trimethylcyclo- hex-6-enealdehyde ...	2490	11,600 ¹	2720	20,100	3860	26,600 ³

* In chloroform : main band only.

¹ Young and Linden, *J. Amer. Chem. Soc.*, 1947, **69**, 2072. ² Andrews, Cristol, Lindenbaum, and Young, *ibid.*, 1945, **67**, 715. ³ Redetermined in these laboratories.

EXPERIMENTAL.

(Absorption spectra, unless stated otherwise, were determined in alcoholic solutions. M. p.s and b. p.s are uncorrected.)

Ethyl α : 1-Epoxy-cyclohexylacetate (I; R = R' = H).—A mixture of ethyl chloroacetate (55 g.) and cyclohexanone (43 g.) was added dropwise to a suspension of finely divided sodium (11 g.) in xylene (165 c.c.) with stirring and cooling (ice-salt). The rate of addition was regulated so that the temperature of the reaction mixture did not exceed 8°. The resulting dark-red clear solution was poured into water, and the organic layer, after repeated washing with water, was dried and evaporated. Distillation of the

residue gave the glycidic ester (37 g., 50%), b. p. 81—83°/0.04 mm., $n_D^{18.5}$ 1.4636 (Newman and Magerlein, *loc. cit.*, give b. p. 115—117°/10 mm., n_D^{20} 1.4600).

2 : 6-Dimethylcyclohex-3-enealdehyde (II).—The aldehyde was prepared by heating crotonaldehyde and piperylene at 170° for 24 hours as described by Holmes *et al.* (*loc. cit.*). The product was carefully distilled through a Dufton column into several fractions, b. p. 77—78°/17 mm., $n_D^{18.5}$ 1.4685—1.4691 (Holmes *et al.*, *loc. cit.*, give b. p. 80—81°/20 mm., n_D^{20} 1.4686). Only one 2 : 4-dinitrophenylhydrazone could be isolated. It crystallised from ethanol in yellow needles, m. p. 165—167° (Found : N, 17.55. $C_{15}H_{18}O_4N_4$ requires N, 17.6%).

2 : 6-Dimethylcyclohexanealdehyde (III).—The unsaturated aldehyde (25 g.) was dissolved in redistilled methyl acetate (30 c.c.), and the solution was shaken for 1½ hours with Raney nickel to remove the small amount of catalyst poison present. The filtered liquid and methyl acetate (20 c.c.) used for washing the nickel were shaken in hydrogen with a palladium-calcium carbonate catalyst (2.0 g.; 6% Pd) at atmospheric pressure until absorption was complete (4510 c.c., corresponding to 1.05 \bar{F}). The catalyst and solvent were removed to give 2 : 6-dimethylcyclohexanealdehyde (16.9 g.; 68%) as a mobile liquid, b. p. 81—83°/17 mm., $n_D^{18.5}$ 1.4536 (Found : C, 77.25; H, 11.8. $C_9H_{16}O$ requires C, 77.1; H, 11.5%). The 2 : 4-dinitrophenylhydrazone crystallised from methanol in yellow needles, m. p. 129—130° (Found : N, 17.55. $C_{15}H_{20}O_4N_4$ requires N, 17.5%).

1-Bromo-2 : 6-dimethylcyclohexanealdehyde (IV).—A solution of bromine (19.5 g.) in chloroform (30 c.c.) was added dropwise to an ice-cooled, stirred suspension of calcium carbonate (8.0 g.) in chloroform (40 c.c.) and the saturated aldehyde (15.6 g.). The bromine was added at such a rate as to keep the reaction mixture at ca. 15°. After another 3 hours' stirring, the mixture was filtered, washed with sodium hydrogen carbonate solution and water, and dried. The solvent was removed under reduced pressure, and the residue distilled. This gave the bromo-aldehyde (12.8 g.; 52%) as an unstable liquid, b. p. 63—66°/0.02 mm., n_D^{23} 1.502 (Found : C, 48.6; H, 7.0. $C_9H_{13}OBr$ requires C, 49.35; H, 6.9%).

2 : 6-Dimethylcyclohex-1-enealdehyde (V).—The bromo-aldehyde (12.6 g.) and diethylaniline (26 g.) were heated to boiling in nitrogen. The solution was refluxed for 2 minutes, and then cooled as rapidly as possible; diethylaniline hydrobromide crystallised out. Water and ether were added, and the excess of base was removed by washing with dilute sulphuric acid. The ethereal extract was washed with sodium hydrogen carbonate solution, dried, and evaporated. The residue was distilled into several fractions, b. p. 92—100°/15 mm., n_D^{23} 1.4935—1.5043. The combined fractions (5.6 g.), consisting predominantly of the unsaturated aldehyde, were converted into the semicarbazone in the usual way. Crystallisation from ethanol then gave the pure semicarbazone of 2 : 6-dimethylcyclohexenealdehyde (6.0 g., 54% based on the bromo-aldehyde) as prisms, m. p. 211° (Found : N, 21.35. $C_{10}H_{17}ON_3$ requires N, 21.5%). Light absorption : see Table.

Regeneration of the aldehyde was effected by heating under reflux a stirred suspension of the semicarbazone in 2*N*-sulphuric acid and light petroleum (b. p. 60—80°). The reaction was rather slow, and was terminated after 115 hours. Some unchanged semicarbazone could be recovered by filtration, and the organic layer after being washed with sodium hydrogen carbonate solution was dried and evaporated. Distillation of the residue gave pure 2 : 6-dimethylcyclohex-1-enealdehyde as a pleasant-smelling liquid, b. p. 96—97°/19 mm., n_D^{19} 1.5042 (Found : C, 78.6; H, 10.35. $C_9H_{14}O$ requires C, 78.2; H, 10.2%). Light absorption : see Table. The 2 : 4-dinitrophenylhydrazone crystallised from ethanol in red needles, m. p. 160—161° (Found : N, 18.1. $C_{15}H_{18}O_4N_4$ requires N, 17.6%). Light absorption : see Table.

1 : 1 : 3-Trimethylbutadiene (2 : 4-Dimethylpenta-1 : 3-diene) (VI).—The hydrocarbon was conveniently prepared by the reaction between mesityl oxide and methylmagnesium iodide, followed by dehydration with a trace of iodine (Jitkov and Bogert, *loc. cit.*). It was obtained in 80-g. quantities (50% yield), b. p. 92.5°/760 mm., $n_D^{19.5}$ 1.4409. Light absorption : Maximum, 2320 Å.; ϵ = 8500. Waterman and De Kok's procedure (*Rec. Trav. chim.*, 1933, 52, 234) was used once, but the main product was a liquid, b. p. 110—112°/25 mm., n_D^{24} 1.4762, showing no appreciable light absorption intensity in the ultra-violet. It was probably the dimer, b. p. 98—100°/12 mm., n_D^{19} 1.4848, described by Grignard (*Ann. Chim.*, 1901, 24, 478).

2 : 2 : 4 : 6-Tetramethylcyclohex-3-enealdehyde (VIII).—1 : 1 : 3-Trimethylbutadiene (15 g.), redistilled crotonaldehyde (12 g., 10% excess), and a trace of quinol were heated in a stainless-steel autoclave for 40 hours at 155—160°. The reaction was repeated on the same scale, and the products were combined. Distillation through a short Vigreux column furnished 2 : 2 : 4 : 6-tetramethylcyclohex-3-enealdehyde (21.5 g., 42%) as a mobile liquid, b. p. 89—92°/13 mm., n_D^{20} 1.4744—1.4750 (Diels and Alder, *Annalen*, 1929, 470, 62, give b. p. 93—95°/18 mm.). When the reaction was carried out at 180° for 7 hours (Diels and Alder, *loc. cit.*), the aldehyde (b. p. 90—95°/18 mm.) could be isolated in only ca. 20% yield. A 76% yield of adduct from crotonaldehyde and 1 : 1 : 2-trimethylbutadiene was reported by Naves and Ardizio (*loc. cit.*) to be obtained by heating the components in light petroleum at 135—140° for 5 hours; the reaction with 1 : 1 : 3-trimethylbutadiene was run under comparable conditions, but only a very small yield of impure adduct was obtained.

The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in yellow needles, m. p. 227—228° (Found : N, 16.2. $C_{17}H_{22}O_4N_4$ requires N, 16.2%). In order to investigate the homogeneity of the aldehyde, the 2 : 4-dinitrophenylhydrazone was prepared from the aldehyde (0.4 g.), and excess of water was added to the reaction mixture to precipitate any methanol-soluble derivative. The precipitate was dissolved in benzene (most of the unchanged reagent remained insoluble and was filtered off), and the solution was poured on a column of alumina (ca. 250 g.). The chromatogram was developed with benzene; the unchanged reagent remained at the top of the column, and a strong well-defined yellow band was obtained, which yielded the normal derivative (m. p. 227—228°). In addition a weak red band

was observed, which yielded a very small quantity (*ca.* 4 mg.) of a red powder. As this could not have been the derivative of the isomeric aldehyde (VII), it was not further investigated.

Sulphur Dehydrogenation of 2 : 2 : 4 : 6-Tetramethylcyclohex-3-enealdehyde (VIII).—The aldehyde (0.6 g.) was heated under reflux with sulphur (0.5 g.) for 5 hours. The volatile products were distilled off at atmospheric pressure, and the yellow distillate was converted into the 2 : 4-dinitrophenylhydrazone in the usual way. Chromatographic analysis as indicated above gave one single well-defined red band, which yielded the 2 : 4-dinitrophenylhydrazone of 2 : 4 : 6-trimethylbenzaldehyde as red plates, *m. p.* 250–251°, from chloroform-ethyl acetate (Found : C, 58.45; H, 5.1. $C_{18}H_{18}O_4N_4$ requires C, 58.5; H, 4.9%). No depression in *m. p.* was observed on admixture with a sample (*m. p.* 250–251°) prepared from authentic 2 : 4 : 6-trimethylbenzaldehyde.

2 : 2 : 4 : 6-Tetramethylcyclohex-3-ene-1-carboxylic Acid (X).—An alcoholic solution of the aldehyde (1.5 g.) was added to aqueous silver nitrate (prepared from $AgNO_3$, 6 g.). The mixture was heated to 50° and excess of sodium hydroxide solution was added dropwise with stirring at this temperature. After being set aside at room temperature with occasional shaking for 40 hours, the mixture was filtered, water and ether were added to the filtrate, and the acidic material was extracted in the usual manner. This yielded the crude solid acid (0.8 g.), which after several crystallisations from aqueous acetic acid formed plates, *m. p.* 85–87° (Found : C, 72.6; H, 10.0. Calc. for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0%). (Naef et Cie., F.P. 672,025, give *m. p.* 82–83°; Diels and Alder, *loc. cit.*, give *m. p.* 88.5–89°.) When the oxidation was carried out completely at room temperature (*cf.*, *inter al.*, Jitkow and Bogert, *loc. cit.*), the yield of acid was considerably reduced.

2 : 2 : 4 : 6-Tetramethylcyclohexanealdehyde (XI).—The unsaturated aldehyde (5.0 g.) in ethanol (30 c.c.), after being freed from catalyst poison by shaking with Raney nickel in the usual way, was shaken in hydrogen with a palladium-calcium carbonate catalyst (0.9 g.; 6% Pd) until absorption was complete (867 c.c., corresponding to 1.15 F). Removal of the catalyst and solvent, followed by distillation of the residue, gave 2 : 2 : 4 : 6-tetramethylcyclohexanealdehyde (3.4 g., 67%), *b. p.* 92–95°/18 mm., n_D^{20} 1.4560 (Found : C, 79.0; H, 12.3. $C_{11}H_{20}O$ requires C, 78.6; H, 11.9%). The 2 : 4-dinitrophenylhydrazone crystallised from ethanol in yellow needles, *m. p.* 159° (Found : N, 16.25. $C_{17}H_{24}O_4N_4$ requires N, 16.1%). When the hydrogenation was carried out on a larger scale, slightly lower yields of the saturated aldehyde were obtained.

1-Bromo-2 : 2 : 4 : 6-tetramethylcyclohexanealdehyde (XII).—A solution of bromine (10.4 g.) in chloroform (15 c.c.) was added dropwise to a stirred and ice-cooled suspension of calcium carbonate (6 g.) in chloroform (30 c.c.) and the saturated aldehyde (10.6 g.), the rate of addition being such that the temperature of the reaction mixture was kept at *ca.* 15°. After being stirred for a further 2 hours at room temperature and being set aside overnight, the mixture was filtered, and the solvent removed from the filtrate under reduced pressure. Distillation of the residue gave an unstable liquid (7.9 g.; 50%), *b. p.* 63–70°/0.01 mm., n_D^{22} 1.496, consisting essentially of the bromo-aldehyde (Found : C, 55.0; H, 8.05. $C_{11}H_{19}OBr$ requires C, 53.45; H, 7.75%).

2 : 2 : 4 : 6-Tetramethylcyclohex-6-enealdehyde (4-Methyl- β -cyclocitral) (XIII).—The bromo-aldehyde (7.8 g.) and diethylaniline (15 g.) were heated to boiling in nitrogen. The solution was refluxed for 2 minutes, and then cooled as rapidly as possible; diethylaniline hydrobromide crystallised out. Working up as before gave crude 4-methyl- β -cyclocitral (3.6 g.) as a pleasant smelling liquid, *b. p.* 100–110°/15 mm., $n_D^{22.5}$ 1.491. Treatment with semicarbazide acetate in aqueous methanol in the usual way yielded the semicarbazone (2.2 g.; 31% based on the bromo-aldehyde), which crystallised from aqueous methanol in plates, *m. p.* 177° (Found : C, 64.8; H, 9.55; N, 19.25. $C_{12}H_{21}ON_3$ requires C, 64.55; H, 9.5; N, 18.8%). Light absorption : see Table. The 2 : 4-dinitrophenylhydrazone crystallized from ethanol in red plates, *m. p.* 131–132° (Found : N, 16.4. $C_{17}H_{22}O_4N_4$ requires N, 16.2%). Light absorption : see Table.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.
CONVERSE MEMORIAL LABORATORY,
HARVARD UNIVERSITY, CAMBRIDGE 38, MASS., U.S.A.

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