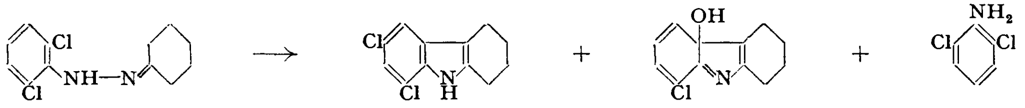
158. *The Fischer Indole Synthesis. Part V. The Cyclisation of Some* cyclo*Hexanone* o-*Substituted Hydrazones.*

By C. S. Barnes, K. H. Pausacker, and (in part) W. E. Badcock.

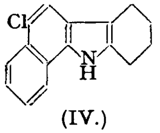
Di-*o*-substituted hydrazones of *cyclo*hexanone yield both 1 : 2 : 3 : 4-tetrahydrocarbazoles (by rearrangement) and 1 : 2 : 3 : 4-tetrahydro*iso*carbazoles. *cyclo*Hexanone *o*-bromophenylhydrazone yields novel products, and camphenilone phenylhydrazone is converted into a compound which is normally postulated as a hypothetical intermediate in the Fischer indole synthesis.

Carlin and Fisher (*J. Amer. Chem. Soc.*, 1948, **70**, 3421) have found that *cyclo*hexanone 2 : 6-dichlorophenylhydrazone (I) is converted, in very small yield (0·3%), into 6 : 8-dichloro-1 : 2 : 3 : 4-tetrahydrocarbazole (II), by use of zinc chloride in nitrobenzene as the catalyst. This cyclisation has been repeated, with aqueous sulphuric acid as the catalyst, and in addition to (II) (24%) both 2 : 6-dichloroaniline (5%) and 8-chloro-1 : 2 : 3 : 4-tetrahydro-12-hydroxy-*iso*carbazole (III) (37%) (cf. Barnes, Pausacker, and Schubert, *J.*, 1949, 1381) have been isolated.

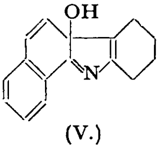


(I.) (II.) (III.)

When *cyclo*hexanone 2 : 6-dibromophenylhydrazone was similarly treated, only 2 : 6-dibromoaniline and 8-bromo-1 : 2 : 3 : 4-tetrahydro-12-hydroxy*iso*carbazole (isolated as its picrate) were separated. Further, *cyclo*hexanone 2-chloro-1-naphthylhydrazone in boiling glacial acetic acid gave both 6-chloro-1 : 2 : 3 : 4-tetrahydro-7 : 8-benzocarbazole (IV) and 1 : 2 : 3 : 4-tetrahydro-12-hydroxy-7 : 8-benzo*iso*carbazole (V). The structure of (IV) was proved both by its dehydrogenation, etc., to 1 : 2-benzocarbazole and by direct synthesis by cyclisation of *cyclo*hexanone 4-chloro-1-naphthylhydrazone.



(IV.)



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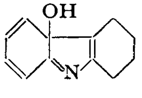
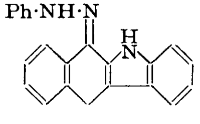


(VI.)



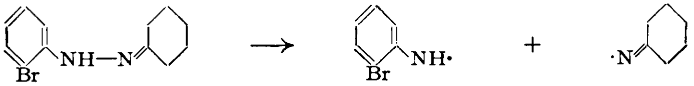
(VII.)

Not only *cyclo*hexanone *o*-halogen-substituted hydrazones may yield 1 : 2 : 3 : 4-tetrahydro*iso*carbazoles : *cyclo*hexanone mesitylhydrazone forms 1 : 2 : 3 : 4-tetrahydro-6 : 8 : 12-trimethyl*iso*carbazole (isolated as its picrate) (unless migration of methyl occurs, which would yield a tetrahydrocarbazole).

It has already been reported (Barnes, Pausacker, and Schubert, *loc. cit.*) that *cyclo*hexanone *o*-chlorophenylhydrazone yields 8-chloro-1 : 2 : 3 : 4-tetrahydrocarbazole and 1 : 2 : 3 : 4-tetrahydro-12-hydroxy*iso*carbazole (VI). When an attempt was made to convert (VI) into the corresponding 12-methoxy-compound (m. p. 146°), by treating it with methylmagnesium iodide followed by excess of methyl iodide, it was found that the product (m. p. 206°) had the correct empirical formula but did not contain a methoxyl group : the structure of this compound is uncertain. Further attempts to prepare (VI) or its analogues by the general method of Bloink and Pausacker (*J.*, 1950, 1328) failed. Thus 2-benzyloxy*cyclo*hexanone phenylhydrazone yielded 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole on sulphuric acid cyclisation, and 2-acetoxy-1 : 2 : 3 : 4-tetrahydro-1-ketonaphthalene gave 1 : 2 : 3 : 4-tetrahydro-1 : 2-diketonaphthalene bisphenylhydrazone in boiling alcohol and 1 : 4-dihydro-1-keto-2 : 3-benzocarbazole phenylhydrazone (VII) when kept in glacial acetic acid.

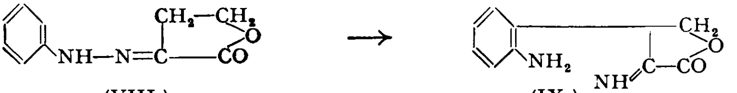
Cyclisation of *cyclo*hexanone *o*-bromophenylhydrazone was also investigated, as it was considered that (VI) would thus be formed, as the corresponding chloro-compound had already yielded this substance. However, different results were obtained. Along with 8-bromo-1 : 2 : 3 : 4-tetrahydrocarbazole (already isolated in the crude form by Barclay and Campbell, *J.*, 1945, 530), three other compounds, (*A*) $C_{12}H_{10}O_2NBr$, m. p. 146°, (*B*) $C_{12}H_{10}O_2NBr$, m. p. 166°, and (*C*) $C_{12}H_8ONBr$, m. p. 253°, were isolated by chromatographic separation. (*A*) displays neither basic nor phenolic properties, whereas (*B*) is soluble in sodium hydroxide solution and is a primary aromatic amine. In addition, (*B*) forms a monoacetyl derivative. When refluxed with alcoholic potash, (*A*) and (*B*) were converted, by loss of water, into (*C*). The substance (*C*) formed a monoacetyl derivative and was soluble in both warm hydrochloric acid and sodium hydroxide solution. When treated with hydrogen in presence of palladised charcoal at 300° it was converted into a strong base, $C_{12}H_{11}N$, m. p. 60°, which formed a picrate. This base did not appear to react with nitrous acid, signifying that it is a tertiary amine. When hydrogenated in the presence of Raney nickel and potassium hydroxide, (*C*) was converted into a basic phenol, $C_{12}H_{11}ON$.

Although the structures of (*A*), (*B*), and (*C*) have not been elucidated, it is of interest that their empirical formulæ * indicate that they may be derived from the *o*-bromoanilino-radical which would be expected if the reaction proceeds according to the mechanism proposed by Pausacker and Schubert (*J.*, 1949, 1384) :



$$2C_6H_5NBr + H_2O \longrightarrow C_{12}H_8ONBr\ (C) + NH_4Br$$
$$2C_6H_5NBr + 2H_2O \longrightarrow C_{12}H_{10}O_2NBr\ (A \text{ or } B) + NH_4Br$$

Finally, results have been obtained similar to those reported by Pleininger (*Ber.*, 1950, **83**, 273), who found that α-ketobutyrolactone phenylhydrazone (VIII) is converted by hydrogen chloride into (IX), which is isomeric with (VIII) and is one of the postulated intermediates in indole formation. We have similarly found that, when camphenilone phenylhydrazone is treated with hydrogen chloride in alcohol, a base is isolated (as its picrate and styphnate) which is isomeric with the original hydrazone and appears to have a structure analogous to that of Pleininger's imine intermediate.



(VIII.) (IX.)

Experimental.

Cyclisation of cyclo*Hexanone* 2 : 6-*Dichlorophenylhydrazone*.—The hydrazone (26·5 g.) was refluxed for 0·5 hour with concentrated sulphuric acid (28 ml.) and water (252 ml.) and then extracted with ether. The ethereal extract (22 g.) was dissolved in benzene and chromatographed on B.D.H. activated alumina. The zone (7·6 g.) which had a yellow fluorescence in ultra-violet light was eluted and treated with picric acid (7·5 g.) in benzene. The orange-red picrate was decomposed with excess of sodium hydroxide and distilled. It had b. p. 180°/0·5 mm., m. p. 67°, mixed m. p. with 6 : 8-dichloro-1 : 2 : 3 : 4-tetrahydrocarbazole 68°, and gave a *picrate*, m. p. 120° (from benzene) (Found : N, 12·1. $C_{12}H_{11}NCl_2,C_6H_3O_7N_3$ requires N, 11·9%), and *styphnate*, m. p. 104° (from light petroleum, b. p. 40—60°) (Found : N, 11·7. $C_{12}H_{11}NCl_2,C_6H_3O_8N_3$ requires N, 11·5%). A small fore-run (0·8 g.; b. p. 84°/1·2 mm.) was identical (mixed m. p.) with 2 : 6-dichloroaniline.

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* It should be noted, however, that Rast molecular-weight determinations for (*B*) and (*C*) were not consistent with the formulæ assigned by us to these substances.

The intermediate dark green zone was discarded and the column eluted with alcohol, a fraction (8·7 g.) being obtained. Treatment of the solution with picric acid (8·4 g.) in benzene gave a *picrate*, red needles (from benzene), m. p. 159° (Found : N, 12·2. $C_{12}H_{12}ONCl,C_6H_3O_7N_3$ requires N, 12·4%). 8-*Chloro*-1 : 2 : 3 : 4-*tetrahydro*-12-*hydroxy*iso*carbazole* was isolated from the picrate by means of sodium hydroxide solution and had m. p. 127° (from light petroleum, b. p. 100—120°) (Found : N, 6·2; Cl, 16·4. $C_{12}H_{12}ONCl$ requires N, 6·3; Cl, 16·0%).

A chloride ion determination on the aqueous portion of the above reaction mixture indicated 33% of hydrolysis.

Cyclisation of cyclo*Hexanone* 2 : 6-*Dibromophenylhydrazone*.—Similar cyclisation of this hydrazone (30·6 g.) gave an ethereal extract (23·6 g.) which was distilled. The first fraction (b. p. 80°/0·2 mm.; m. p. 84°; 4·6 g.) was identified as 2 : 6-dibromoaniline (mixed m. p.). The second fraction (b. p. 150—155°/0·25 mm.; 6·7 g.) was treated with picric acid, to form 8-*bromo*-1 : 2 : 3 : 4-*tetrahydro*-12-*hydroxy*iso*carbazole picrate*, m. p. 130° (reddish-brown needles from benzene) (Found : N, 11·6. $C_{12}H_{12}ONBr,C_6H_3O_7N_3$ requires N, 11·3%). A bromide ion analysis on the aqueous portion of the mixture indicated 63% of hydrolysis.

Cyclisation of cyclo*Hexanone* 2-*Chloro*-1-*naphthylhydrazone*.—The hydrazone (33 g.) was refluxed (1·5 hour) with glacial acetic acid (280 ml.). The acetic acid was distilled on the water-bath (water-pump), and the residue dissolved in a small volume of benzene and chromatographed on alumina, with benzene as eluent. When this solution was evaporated, 6-*chloro*-1 : 2 : 3 : 4-*tetrahydro*-7 : 8-*benzocarbazole* (IV) was obtained, having m. p. 119° (from light petroleum, b. p. 60—90°) (Found : C, 75·4; H, 5·7; N, 5·3. $C_{16}H_{14}NCl$ requires C, 75·2; H, 5·5; N, 5·5%). The *picrate* had m. p. 168° (from benzene) (Found : N, 12·0. $C_{16}H_{14}NCl,C_6H_3O_7N_3$ requires N, 11·6%). When (IV) was treated with hydrogen and palladised charcoal at 300°, 1 : 2-benzocarbazole was obtained in excellent yield, having m. p. 228° (from light petroleum, b. p. 100—120°) (Found : N, 7·0. Calc. for $C_{16}H_{11}N$: N, 6·5%) [*picrate*, m. p. 184° (from benzene–light petroleum, b. p. 60—90°) (Found : N, 13·0. $C_{16}H_{11}N,C_6H_3O_7N_3$ requires N, 12·6%)].

When the column was finally eluted with benzene–ethyl alcohol (5%), 12-*hydroxy*-1 : 2 : 3 : 4-*tetrahydro*-7 : 8-*benzo*iso*carbazole*, m. p. 320° (from pyridine–ethyl alcohol), was deposited (Found : C, 81·3; H, 6·1; N, 6·0. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 5·9%).

The structure of (IV) was proved by synthesis : 1-chloro-4-nitronaphthalene was reduced with hydrogen in the presence of Raney nickel (yield, 90%), and the resultant 4-chloro-1-naphthylamine was converted into the corresponding hydrazine by Carlin and Fisher's method (*loc. cit.*) (yield of crude hydrazine, 75%). This (1·5 g.) and *cyclo*hexanone (1 g.) were refluxed for 1 hour with glacial acetic acid (30 ml.). On evaporation, (IV) (1·6 g.) was obtained, having m. p. and mixed m. p. with the product obtained above, 121°.

Cyclisation of cyclo*Hexanone Mesitylhydrazone*.—The above hydrazone was cyclised with glacial acetic acid, and the residue, after removal of the acetic acid under reduced pressure, was treated with picric acid in benzene. Black crystals of (?) 1 : 2 : 3 : 4-*tetrahydro*-6 : 8 : 12-*trimethyl*iso*carbazole picrate*, m. p. 170—171° (from benzene), were obtained (Found : C, 57·1; H, 5·1; N, 12·7. $C_{15}H_{19}N,C_6H_3O_7N_3$ requires C, 57·2; H, 5·0; N, 12·7%).

Reaction of 1 : 2 : 3 : 4-*Tetrahydro*-12-*hydroxy*iso*carbazole* (VI) *with Methylmagnesium Iodide and Methyl Iodide*.—A filtered solution of methylmagnesium iodide [prepared from magnesium (0·5 g.), methyl iodide (1 ml.), and ether (10 ml.)] was added to a solution of (VI) (0·2 g.) in ether (10 ml.). After 1 hour's refluxing, methyl iodide (5 ml.) was added and refluxing continued for 2·5 hours. The solution was washed with ammonium chloride solution and evaporated, a *compound*, m. p. 206° (from ethyl acetate), being obtained (Found : C, 77·1; H, 7·3; N, 6·9; OMe, 0. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

Cyclisation of 2-*Benzyloxy*cyclo*hexanone Phenylhydrazone*.—2-*Benzyloxy*cyclo*hexanone*, prepared by heating 2-chloro*cyclo*hexanone with sodium benzyloxide in anhydrous benzene, had b. p. 173—175°/21 mm. (Found : C, 76·8; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). When this was condensed with phenylhydrazine and cyclised with sulphuric acid, the product consisted almost entirely of neutral material—a mixture of benzyl alcohol and 1 : 2 : 3 : 4-tetrahydro-1-ketocarbazole (m. p. and mixed m. p. 168°).

Reactions of 2-*Acetoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*ketonaphthalene with Phenylhydrazine*.—A mixture of the ketone (1·0 g.) and phenylhydrazine (1·5 g.) in acetic acid (10 ml.) gradually deposited bright yellow needles (1·0 g.) of 1 : 4-*dihydro*-1-*keto*-2 : 3-*benzocarbazole phenylhydrazone*, m. p. 175° (from acetic acid) (Found : N, 12·9. $C_{22}H_{17}N_3$ requires N, 13·0%).

When the ketone (1·0 g.) was refluxed (3 days) with phenylhydrazine (1·6 g.) in ethyl alcohol (10 ml.), ammonia was evolved, but the only product isolated was 1 : 2 : 3 : 4-*tetrahydro*-1 : 2-*diketonaphthalene bisphenylhydrazone* which separated from the cooled mixture as yellow needles, m. p. 126° (from acetic acid) (Found : C, 77·2; H, 5·8; N, 16·1. $C_{22}H_{20}N_4$ requires C, 77·6; H, 5·9; N, 16·5%).

These results differ from those obtained by Bloink and Pausacker (*loc. cit.*).

Cyclisation of cyclo*Hexanone* o-*Bromophenylhydrazone*.—This hydrazone (48 g.) was refluxed for 10 minutes with a mixture of concentrated sulphuric acid (50 ml.) and water (450 ml.). The product was extracted with ether and basification of the acid solution gave an oil which was acetylated, forming N-*acetyl*-o-*bromophenylhydrazine*, m. p. 156° (from water) (Found : C, 41·6; H, 4·2; N, 12·1. $C_8H_9ON_2Br$ requires C, 41·5; H, 3·9; N, 12·2%). The ethereal extract, a dark red oil (46 g.), was dissolved in dry benzene and passed through a column (24″ × 1·5″) packed with activated alumina (Peter Spence; type H 100/200). The column was eluted with benzene, and the eluate, when kept, deposited a solid (*A*) (3·2 g.; m. p. 146°). Concentration in the air gave a second solid (*B*) (3·0 g.; m. p. 166°). The column was then eluted with alcohol–benzene (1 : 20), giving a third substance (*C*) (2·15 g.; m. p. 252°). After (*A*) and (*B*) had been filtered off, the filtrate was evaporated to dryness, yielding a dark red oil (34 g.). A portion of this with picric acid yielded 8-*bromo*-1 : 2 : 3 : 4-*tetrahydrocarbazole picrate*, m. p. 133° (red needles from benzene) (Found : C, 45·4; H, 3·5; N, 12·0. $C_{12}H_{12}NBr,C_6H_3O_7N_3$ requires C, 45·1; H, 3·1; N, 11·7%), which with sodium hydroxide solution afforded 8-*bromo*-1 : 2 : 3 : 4-*tetrahydrocarbazole*, m. p. 57° [prisms from light petroleum (b. p. 40—60°)] (Found : N, 6·1. $C_{12}H_{12}NBr$ requires N, 5·6%).

When (*A*) or (*B*) (0·2 g.) was refluxed for 2 hours with ethyl alcohol (10 ml.) and potassium hydroxide (0·6 g.), (*C*) (identified by m. p. and mixed m. p.) was formed.

Chemical properties of (C). Substance (*C*) crystallised as needles (from benzene), m. p. 253° [Found : C, 54·5; H, 2·9; N, 5·2; Br, 29·2; *M* (Rast), 210. $C_{12}H_8ONBr$ requires C, 54·9; H, 3·1; N, 5·3; Br, 30·5%; *M*, 262], and gave a *semipicrate* (from benzene), m. p. 223—224° (Found : C, 48·1; H, 3·1; N, 9·5. $2C_{12}H_8ONBr,C_6H_3O_7N_3$ requires C, 47·8; H, 2·5; N, 9·3%). It was insoluble in cold water, dilute hydrochloric acid, or sodium hydroxide solution, but soluble in all these solvents when heated, a precipitate appearing when the aqueous and hydrochloric acid solutions were cooled. When the sodium hydroxide solution was acidified, a heavy precipitate was deposited. No reaction was noted with nitrous acid, followed by alkaline β-naphthol.

When (*C*) (0·2 g.) was heated at 280—300° for 3 hours with palladised charcoal (0·2 g.) in a stream of hydrogen, a white sublimate of a hydrobromide was obtained. This was extracted with water, the solution filtered, and the filtrate evaporated to dryness. The residue was treated with sodium hydroxide solution, and the *base* extracted with light petroleum (b. p. 40—60°). When purified by sublimation in a high vacuum, it had m. p. 60° (Found : C, 84·8; H, 6·8; N, 8·2. $C_{12}H_{11}N$ requires C, 85·2; H, 6·5; N, 8·3%). It dissolved readily in dilute hydrochloric acid and did not react with sodium nitrite followed by alkaline β-naphthol. It formed a *picrate* (yellow needles from water), m. p. 190° (Found : C, 54·3; H, 3·5; N, 14·0. $C_{12}H_{11}N,C_6H_3O_7N_3$ requires C, 54·2; H, 3·5; N, 14·1%). It gave a black tar when heated with benzenesulphonyl chloride and sodium hydroxide.

When (*C*) (0·4 g.) was shaken in an atmosphere of hydrogen at room temperature and pressure with Raney nickel (4 ml.) and potassium hydroxide (0·25 g.) in ethyl alcohol (20 ml.), 1·9 moles of hydrogen were absorbed. The *product*, m. p. 341° (from ethyl alcohol), which was soluble in both sodium hydroxide solution and hydrochloric acid, gave a red colour with ferric chloride in alcohol (Found : C, 77·9; H, 6·1; N, 7·3. $C_{12}H_{11}ON$ requires C, 77·7; H, 5·9; N, 7·6%).

Acetylation of (*C*) in pyridine–acetic anhydride and extraction with ether gave a *product*, m. p. 154° (from *n*-hexane), soluble in hydrochloric acid (Found : C, 55·7; H, 3·1; N, 5·0; Ac, 15·9. $C_{14}H_{10}O_2NBr$ requires C, 55·2; H, 3·3; N, 4·6; Ac, 14·2%).

Chemical properties of (B). Substance (*B*) was not isolated in every experiment. It formed needles (from benzene), m. p. 166° [Found : C, 51·5; H, 3·9; N, 5·1; Br, 23·8; *M* (Rast), 208. $C_{12}H_{10}O_2NBr$ requires C, 51·4; H, 3·6; N, 5·0; Br, 28·6%; *M*, 280). . It was insoluble in water or dilute hydrochloric acid in the cold, but soluble in water on warming and gave an oil when heated with hydrochloric acid. It dissolved in sodium hydroxide solution, forming a lemon-yellow solution which gave a heavy precipitate on the addition of hydrochloric acid. When treated with nitrous acid and added to alkaline β-naphthol, a deep-red solution was obtained, indicating a primary aromatic amine soluble in sodium hydroxide. It gave neither a picrate nor a positive ferric chloride test. With pyridine–acetic anhydride it gave a *compound*, m. p. 124° (from light petroleum, b. p. 60—90°) (Found : C, 52·3; H, 4·2; N, 4·2; Ac, 15·3. $C_{14}H_{12}O_3NBr$ requires C, 52·2; H, 3·7; N, 4·4; Ac, 13·4%).

Chemical properties of (A). The substance had m. p. 146° (deflagration) (from dioxan) (Found : C, 51·2; H, 4·0; N, 4·8; Br, 28·6. $C_{12}H_{10}O_2NBr$ requires C, 51·4; H, 3·6; N, 5·0; Br, 28·6%). It was insoluble in hot or cold water, cold hydrochloric acid, or cold sodium hydroxide solution, but gave an oil when boiled with either of the last two reagents. It did not react with ferric chloride or nitrous acid.

Cyclisation of Camphenilone Phenylhydrazone.—Camphenilone (3·0 g.) and phenylhydrazine (2·4 g.) were heated on a boiling water-bath for 4 hours, under reduced pressure, in the presence of a drop of acetic acid. *Camphenilone phenylhydrazone* (4·0 g.) (b. p. 137—40°/0·2 mm.) was obtained (Found : C, 78·6; H, 8·7; N, 12·8. $C_{15}H_{20}N_2$ requires C, 78·9; H, 8·8; N, 12·3%). The hydrazone (3·9 g.) was dissolved in magnesium-dried ethyl alcohol (15 ml.) cooled in ice, and saturated with hydrogen chloride. After being cooled for 1 hour, the mixture was set aside over-night at room temperature, whereafter a solid had separated. After removal of the alcohol under reduced pressure, water was added and the neutral substance (3·2 g.) was extracted with ether. The aqueous filtrate was made alkaline with sodium hydroxide solution, ammonia being evolved, and the precipitated organic base (0·5 g.) was extracted with ether. It formed a *picrate*, m. p. 144° (decomp.) (from light petroleum, b. p. 80—100°) (Found : C, 55·0; H, 5·1. $C_{15}H_{20}N_2,C_6H_3O_7N_3$ requires C, 55·1; H, 5·1%) and a *styphnate*, m. p. 160° (decomp.) (from light petroleum, b. p. 100—120°) (Found: C, 52·9; H, 4·8; N, 14·3. $C_{15}H_{20}N_2,C_6H_3O_8N_3$ requires C, 53·3; H, 4·9; N, 14·8%).

Analyses are by Drs. Strauss and Weiler, Oxford, and Dr. Zimmermann, Melbourne. Determinations of bromine and acetyl were approximate only, but suffice to show the number of atoms present.

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