160. *The Action of Grignard Reagents on Methyl* r-*Tropate and on Methyl Atropate.*

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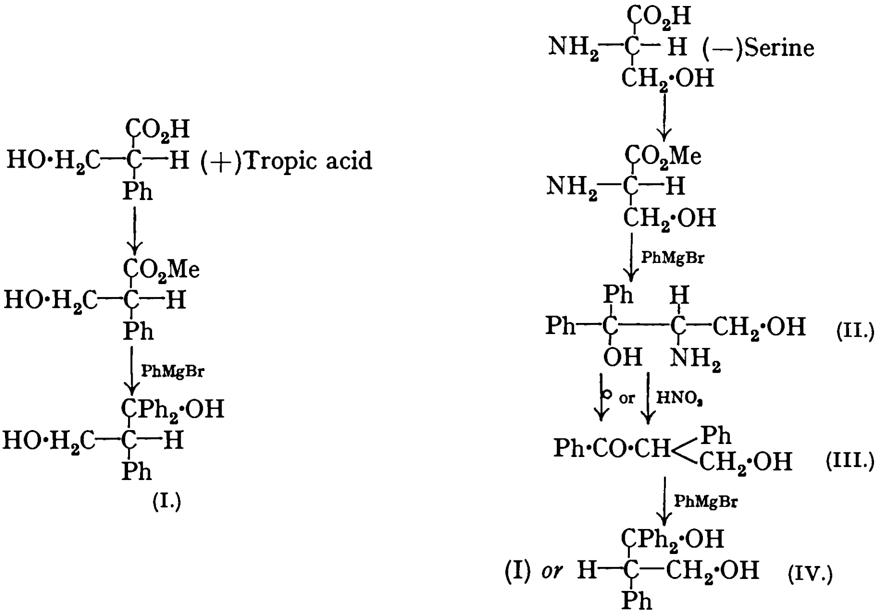
The action of phenylmagnesium bromide on methyl *r*-tropate took an unexpected course, since the product was *r*-benzyldeoxybenzoin. The analogue of the latter compound, namely, *dl*-3-phenylpentan-2-one, was formed when methyl *r*-tropate was acted on by methylmagnesium iodide, but r-*αγ-dihydroxy-β-phenyl-γγ-dimethylpropane* was also formed. The mechanism of the production of the two ketones is discussed.

The action of phenylmagnesium bromide on methyl atropate gave *r*-benzyldeoxybenzoin, and the action of methylmagnesium iodide on the same ester gave *dl*-3-phenylpentan-2-one.

THE original object of this research was to make a configurational study on the following lines, the compounds in each case being optically active :



$$\begin{array}{c} \mathrm{CO_2H} \\ \mathrm{HO{\cdot}H_2C{-}\overset{|}{\underset{|}{C}}{-}H} \ \text{(+)Tropic acid} \\ \mathrm{Ph} \end{array} \xrightarrow{} \begin{array}{c} \mathrm{CO_2Me} \\ \mathrm{HO{\cdot}H_2C{-}\overset{|}{\underset{|}{C}}{-}H} \\ \mathrm{Ph} \end{array} \xrightarrow{\mathrm{PhMgBr}} \begin{array}{c} \mathrm{CPh_2{\cdot}OH} \\ \mathrm{HO{\cdot}H_2C{-}\overset{|}{\underset{|}{C}}{-}H} \\ \mathrm{Ph} \end{array} \quad \text{(I.)}$$

$$\begin{array}{c} \mathrm{CO_2H} \\ \mathrm{NH_2{-}\overset{|}{\underset{|}{C}}{-}H} \ \text{(−)Serine} \\ \mathrm{CH_2{\cdot}OH} \end{array} \xrightarrow{} \begin{array}{c} \mathrm{CO_2Me} \\ \mathrm{NH_2{-}\overset{|}{\underset{|}{C}}{-}H} \\ \mathrm{CH_2{\cdot}OH} \end{array} \xrightarrow{\mathrm{PhMgBr}} \begin{array}{c} \mathrm{Ph} \quad\ \mathrm{H} \\ \mathrm{Ph{-}\overset{|}{\underset{|}{C}}{-}{-}\overset{|}{\underset{|}{C}}{-}CH_2{\cdot}OH} \\ \mathrm{OH} \quad \mathrm{NH_2} \end{array} \ \text{(II.)}$$

$$\xrightarrow{\mathrm{O}\ \text{or}\ \mathrm{HNO_2}} \mathrm{Ph{\cdot}CO{\cdot}CH}{<}\begin{array}{l}\mathrm{Ph}\\ \mathrm{CH_2{\cdot}OH}\end{array} \ \text{(III.)} \xrightarrow{\mathrm{PhMgBr}} \text{(I) } or \ \begin{array}{c} \mathrm{CPh_2{\cdot}OH} \\ \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}CH_2{\cdot}OH} \\ \mathrm{Ph} \end{array} \ \text{(IV.)}$$

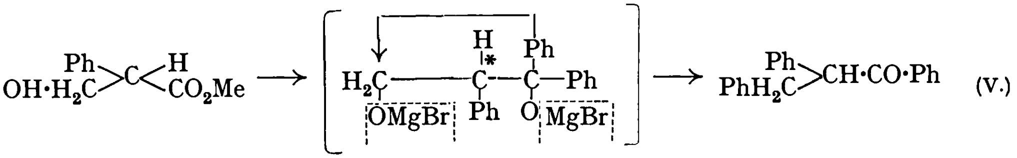
A configurational change might possibly occur during the semipinacolinic deamination of (II). By analogy with the formation of (+)methyldeoxybenzoin from (+)alanine and of (+)benzyldeoxybenzoin from (−)phenylalanine (McKenzie, Roger, and Wills, J., 1926, 779), where the possibility of a Walden inversion was suggested (compare Bernstein and Whitmore, *J. Amer. Chem. Soc.*, 1939, **61**, 1324), (III) would presumably be either dextrorotatory or lævorotatory, and by the action of phenylmagnesium bromide would thus give either (I) or (IV).

Now, assuming on the evidence available in the literature that (+)tropic acid has the same configuration as (−)serine, the sign of rotation of the glycol derived from (III) would indicate whether or not a Walden inversion had occurred during the semipinacolinic deamination in question.

As a preliminary step to this enquiry we examined the action of phenylmagnesium bromide on methyl *r*-tropate, and were surprised to find that the product was not *r*-αγ-dihydroxy-βγγ-triphenylpropane [the optically inactive isomeride of (I)]. The crystalline compound obtained melted at 120—121°, and its analysis agreed with the formula $C_{21}H_{18}O$, and not with $C_{21}H_{20}O_2$. It gave a 2 : 4-*dinitrophenylhydrazone*, and formed r-*β-hydroxy-αββ-triphenyl-α-benzylethane* on treatment with phenylmagnesium bromide. It was identified as *r*-benzyldeoxybenzoin (V). Several preparations were carried out in which the additive complex from the Grignard reaction was decomposed by ice and dilute sulphuric acid. But the result cannot be ascribed to the dehydrating effect of the latter acid on the glycol itself, since *r*-benzyldeoxybenzoin was also formed when a mixture of ammonium chloride and ammonia was used to decompose the complex.

The simplest mechanism to account for the formation of *r*-benzyldeoxybenzoin (V) involves the intramolecular migration of a phenyl group on the lines :

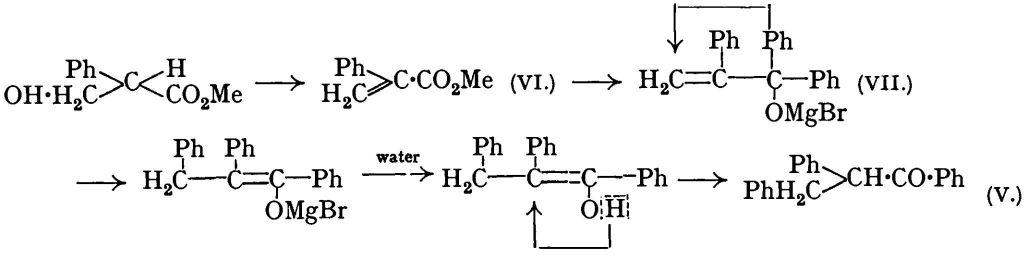
Scheme I.



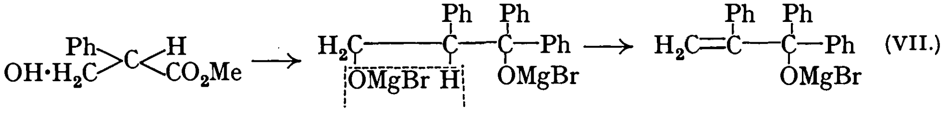
It will be noticed that the central carbon atom * possesses a dissymmetrical environment. The validity or otherwise of the above formulation was accordingly tested by acting on methyl (—)tropate with phenylmagnesium bromide. This action gave benzyldeoxybenzoin, which was, however, optically inactive. If the above scheme were correct, an optically active ketone would have been expected as the product. Besides, the scheme is not in harmony with the strong saturation capacity of the phenyl group, and we regard it as untenable.

The following representation is suggested :

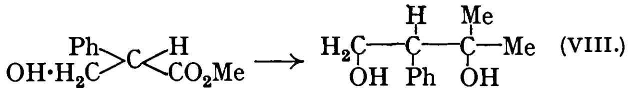
Scheme II.



Here again, a phenyl group is depicted as migrating. Support was given to this scheme when the action of phenylmagnesium bromide on methyl atropate (VI) was also found to give (V) as the product. The conversion of methyl *r*-tropate into (VI) is likely enough, since numerous cases are known from the literature where a Grignard reagent acts as a dehydrating agent. It should be borne in mind, however, that *r*-tropic acid is not itself, as we find, appreciably dehydrated to atropic acid by phenylmagnesium bromide at the ordinary temperature. Even, however, if the assumption is made that the ester itself does not undergo dehydration, the same unstable complex (VII) as is depicted above might be formed by the elimination of magnesium hydroxybromide from the additive complex as follows :

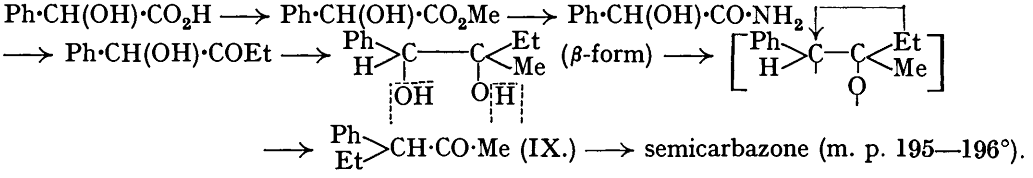


Preliminary experiments on the action of methylmagnesium iodide on methyl *r*-tropate gave r-*αγ-dihydroxy-β-phenyl-γγ-dimethylpropane*, the action in this case taking the normal course :



On dehydration of this glycol, however, with dilute sulphuric acid, the resulting oil did not form either a semicarbazone or a 2 : 4-dinitrophenylhydrazone. There was thus no evidence of the formation of *dl*-3-phenylpentan-2-one (IX), the analogue of benzyldeoxybenzoin.

An interesting point emerged when the action of methylmagnesium iodide on methyl *r*-tropate was examined further. In an endeavour to improve the yield of the glycol, the semi-solid mass obtained from the ethereal solution after decomposition of the additive complex was distilled under a high vacuum. The first fraction was a mobile oil with a characteristic odour of geraniums. This oil was proved to contain (IX), and it formed a semicarbazone (m. p. 195—196°) which was synthesised from *r*-mandelic acid on the following lines :

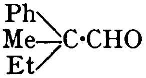


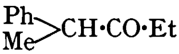
$$Ph\cdot CH(OH)\cdot CO_2H \longrightarrow Ph\cdot CH(OH)\cdot CO_2Me \longrightarrow Ph\cdot CH(OH)\cdot CO\cdot NH_2 \longrightarrow Ph\cdot CH(OH)\cdot COEt \longrightarrow \begin{matrix}Ph\\H\end{matrix}\!>\!\underset{OH}{C}\!-\!\underset{OH}{C}\!<\!\begin{matrix}Et\\Me\end{matrix}\ (\beta\text{-form}) \longrightarrow \left[\begin{matrix}Ph\\H\end{matrix}\!>\!C\!-\!\underset{O}{C}\!<\!\begin{matrix}Et\\Me\end{matrix}\right] \longrightarrow \begin{matrix}Ph\\Et\end{matrix}\!>\!CH\cdot CO\cdot Me\ (IX.) \longrightarrow \text{semicarbazone (m. p. 195—196°)}.$$

(IX) was formed by the semipinacolinic dehydration of the β-form of the glycol, the ethyl group migrating in preference to the methyl (compare Tiffeneau, Lévy, and Jullien, *Bull. Soc. chim.*, 1931, **49**, 1788).

The only other possible products of the dehydration are *dl*-phenylmethylethylacetaldehyde (X) and *dl*-2-phenylpentan-3-one (XI) :

(X.)

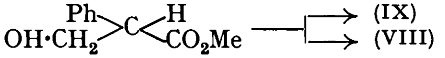




(XI.)

It is highly improbable that (X) could be formed, since the dehydration was carried out by concentrated sulphuric acid. Also, the semicarbazones of (X) and (XI) melt at 152° and 136° respectively (Lévy and Tabart, *Bull. Soc. chim.*, 1931, **49**, 1785), values which are divergent from that of the semicarbazone of (IX).

Thus, the action of methylmagnesium iodide on methyl *r*-tropate proceeds in the two directions :



$$\begin{matrix}Ph\\OH\cdot CH_2\end{matrix}\!>\!C\!<\!\begin{matrix}H\\CO_2Me\end{matrix} \longrightarrow \begin{matrix}\longrightarrow (IX)\\ \longrightarrow (VIII)\end{matrix}$$

The formation of (IX) cannot be attributed to the decomposition of (VIII) by heat, since the latter can be distilled without even a trace of (IX) being detected by its characteristic odour.

On boiling an ethereal solution of the glycol (VIII) with the Grignard reagent from methyl iodide for 30 minutes, the presence of (IX) was detected by the isolation of the semicarbazone. It is thus probable that the complex $H_2\underset{OMgBr}{C}\!-\!\overset{Ph}{\underset{H}{C}}\!-\!\overset{Me}{\underset{OMgBr}{C}}\!-\!Me$ had been formed to give $H_2C\!=\!\overset{Ph}{C}\!-\!C\!\begin{matrix}\diagup Me\\ -Me\\ \diagdown OMgBr\end{matrix}$, a structure which is comparable with (VII). In support of this view, the action of methylmagnesium iodide on methyl atropate led to the formation of *dl*-3-phenylpentan-2-one, which was identified by its semicarbazone :

$$\begin{matrix}Ph\\H_2C\end{matrix}\!\geqslant\!C\cdot CO_2Me\ (VI.) \longrightarrow \begin{matrix}Ph\\Et\end{matrix}\!>\!CH\cdot CO\cdot Me\ (IX.)$$

The formation of (IX) from (VI) is regarded as taking a similar course to the formation of (V) from (VI) which is depicted in Scheme II.

EXPERIMENTAL.

Ethyl formylphenylacetate was slowly reduced in ethereal solution by aluminium amalgam (McKenzie and Wood, J., 1919, **115**, 828; von Braun, *Ber.*, 1920, **53**, 1409), and the product was then saponified by N-sodium hydroxide at the ordinary temperature. The yields of *r*-tropic acid, m. p. 117·5—118·5°, were better than those recorded formerly, and amounted to 50% to 56%, calculated from the ethyl formylphenylacetate used. The acid was then converted into its methyl ester, m. p. 36—37·5°.

Action of Phenylmagnesium Bromide on Methyl r-*Tropate.*—An ethereal solution of the ester (7·5 g.) was gradually added to the Grignard reagent prepared from bromobenzene (40 g.). After boiling for 10 hours, decomposition was effected by ice, ammonium chloride and ammonia. The ether was expelled from the ethereal layer, and the diphenyl removed by distillation in steam. The resulting solid (5 g.) was nearly pure, and was crystallised from ethyl alcohol, *r*-benzyldeoxybenzoin separating in glassy needles (Found : C, 88·6 ; H, 6·0. Calc. for $C_{21}H_{18}O$: C, 88·1 ; H, 6·3%). It had m. p. 120—121°, alone or mixed with a specimen prepared by the action of benzyl bromide on deoxybenzoin (compare Meyer and Oelkers, *Ber.*, 1888, **21**, 1300). Its 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl alcohol in orange-coloured prisms, m. p. 163—164° (Found : C, 69·9 ; H, 4·6. $C_{27}H_{22}O_4N_4$ requires C, 69·5 ; H, 4·8%). The same compound was also obtained from *r*-benzyldeoxybenzoin prepared from deoxybenzoin, and there was no depression of m. p. when both samples were mixed.

Action of Phenylmagnesium Bromide on r-*Benzyldeoxybenzoin.*—An ethereal solution of *r*-benzyldeoxybenzoin (5 g.), obtained from methyl *r*-tropate, was added gradually to the Grignard reagent prepared from bromobenzene (11·5 g.). Boiling, 11 hours; decomposition with ice and dilute sulphuric acid. After removal of the diphenyl, the product was crystallised from ethyl alcohol. Yield, 4 g.

r-β-*Hydroxy*-αββ-*triphenyl*-α-*benzylethane* formed transparent needles, m. p. 146—147° (Found : C, 88·7 ; H, 6·8. $C_{27}H_{24}O$ requires C, 89·0 ; H, 6·6%).

By the action of light on a mixture of benzophenone and dibenzyl, Sernagiotto (*Gazzetta*, 1920, **50**, 226) obtained a compound, m. p. 165°, which was provisionally designated as triphenylbenzylethanol.

Action of Phenylmagnesium Bromide on Methyl (—)*Tropate.*—The methyl (—)tropate used had $n_D^{18°}$ 1·5219, b. p. 157—159°/16 mm., and $[\alpha]_{5461}^{17°}$ $-54·1°$ ($c = 6·578$) in acetone. It was not, however, optically pure, since *methyl* (+)*tropate*, prepared in this laboratory by Dr. Alex. Ritchie from optically pure (+)tropic acid (McKenzie and Wood, *loc. cit.*), has $n_D^{18°}$ 1·5203, b. p. 162—163°/20 mm., and $[\alpha]_D^{20°}$ $+ 69·9°$, $[\alpha]_{5461}^{20°}$ $+ 83·3°$ ($c = 4·947$) in acetone (Found : C, 66·3 ; H, 7·1. $C_{10}H_{12}O_3$ requires C, 66·6 ; H, 6·7%).

An ethereal solution of the ester (4 g.), b. p. 157—159°/16 mm., was added gradually to the Grignard reagent prepared from bromobenzene (40 g.). Boiling, 12 hours; treatment as usual. The dried ethereal layer, which was optically inactive, gave a semi-solid mass, which was crystallised from ethyl alcohol, and gave needles (2·5 g.) exhibiting no optical activity when examined in acetone for λ 5461. The product was *r*-benzyldeoxybenzoin, m. p. 120—121° alone or mixed with an authentic sample.

Action of Methylmagnesium Iodide on Methyl r-*Tropate.*—An ethereal solution of the ester (8·7 g.) was gradually added to the Grignard reagent prepared from methyl iodide (34·5 g.). Boiling, 12 hours; treatment as usual. The semi-solid oil (4·5 g.) obtained was crystallised once from chloroform, and then thrice from light petroleum (b. p. 80—100°). Yield, 2·5 g.

Several other experiments under varying conditions failed to give an increased yield.

r-αγ-*Dihydroxy*-β-*phenyl*-γγ-*dimethylpropane* formed hard prisms, m. p. 80—81° (Found : C, 73·5 ; H, 9·3. $C_{11}H_{16}O_2$ requires C, 73·3 ; H, 9·0%).

The glycol (2 g.) was boiled with dilute sulphuric acid for 6 hours. On cooling, the mixture was poured into ice-cold water and extracted with ether. The resulting oil (1·25 g.) gave neither a semicarbazone nor a 2 : 4-dinitrophenylhydrazone.

A by-product from the action of methylmagnesium iodide on methyl *r*-tropate was obtained as follows : Ester (11 g.) ; Grignard reagent from methyl iodide (100 g.) ; heating, 24 hours; treatment as usual. The resulting golden-coloured oil (14 g.) was distilled under a high vacuum. The fraction (A), b. p. 90—120°, was a mobile oil (3·3 g.) with a characteristic odour of geraniums. The fraction (B), b. p. 120—150°, was very viscous, and solidified gradually to give *r*-αγ-dihydroxy-β-phenyl-γγ-dimethylpropane after one crystallisation from chloroform–light petroleum. On treatment with semicarbazide hydrochloride, (A) gave *r*-3-phenylpentan-2-one semicarbazone crystallising from methyl alcohol in transparent leaflets, m. p. 195—196° (Found : C, 65·8 ; H, 7·3. Calc. for $C_{12}H_{17}ON_3$: C, 65·8 ; H, 7·8%). Tiffeneau and Lévy (*Bull. Soc. chim.*, 1923, **33**, 759) give m. p. 189°.

No trace of the ketone was detected when 4 g. of *r*-αγ-dihydroxy-β-phenyl-γγ-dimethylpropane were distilled under high vacuum. The distillate (3·8 g.) consisted of the unchanged glycol alone, and no odour of geraniums was perceptible.

The above semicarbazone was synthesised as follows : *dl*-Phenylpropionylcarbinol (13 g.) was gradually added to the Grignard reagent prepared from methyl iodide (32 g.). Heating, 12 hours; treatment as usual. When the resulting solid (12 g.) was crystallised from light petroleum (b. p. 80—100°), *r*-αβ-dihydroxy-α-phenyl-β-methylbutane (β-form) separated in needles, m. p. 71—72°, whereas Tiffeneau and Lévy (*Compt. rend.*, 1924, **178**, 1724) give m. p. 73°. The latter glycol (2 g.) was triturated with concentrated sulphuric acid (10 c.c.) at the ordinary temperature. After 2 hours, the mixture was poured into ice-cold water, and extracted with ether. The resulting yellowish oil, which had the odour of geraniums, was converted into the semicarbazone, m. p. 195—196°, alone or mixed with the semicarbazone from *dl*-3-phenylpentan-2-one obtained from methyl *r*-tropate.

Action of Methylmagnesium Iodide on r-*αγ-Dihydroxy-β-phenyl-γγ-dimethylpropane.*—An ethereal solution of the glycol (1·5 g.) was added gradually to the Grignard reagent prepared from methyl iodide (6 g.). After boiling for ½ hour, the complex was decomposed with ice and dilute sulphuric acid, and kept over-night before the layers were separated. The ether was expelled from the ethereal solution, and the resulting oil was distilled under a high vacuum. The second fraction (1 g.), which was viscous, solidified on cooling, and after one crystallisation from chloroform-light petroleum gave the original glycol. The first fraction, which was mobile, had a characteristic odour of geraniums and on treatment with semicarbazide hydrochloride gave the semicarbazone (m. p. 195—196°) of *dl*-3-phenylpentan-2-one.

Action of Phenylmagnesium Bromide on Methyl Atropate.—Atropic acid, prepared from *r*-atrolactinic acid according to McKenzie and Wood (*loc. cit.*), was converted into its methyl ester, b. p. 106—109°/12 mm. (Found : C, 74·3; H, 6·3. Calc. for $C_{10}H_{10}O_2$: C, 74·1; H, 6·2%). Baker and Eccles (J., 1927, 2129) give b. p. 95—98°/6 mm.

An ethereal solution of methyl atropate (5 g.) was added gradually to the Grignard reagent prepared from bromobenzene (20 g.). Heating, 11 hours; treatment as usual. When the resulting viscous solid was crystallised from ethyl alcohol, glassy needles of *r*-benzyldeoxybenzoin (3·6 g.) separated. The m. p. was 119—120°, alone or mixed with an authentic sample.

Action of Methylmagnesium Iodide on Methyl Atropate.—An ethereal solution of the ester (4 g.) was added gradually to the Grignard reagent prepared from methyl iodide (14 g.). Heating, 8 hours; treatment as usual. The resulting yellow oil was distilled. The fraction (1·8 g.) boiling up to 110°/12 mm. had the odour of geraniums, and gave a semicarbazone which crystallised from methyl alcohol in transparent leaflets, m. p. 195—196°, alone or mixed with the semicarbazone of *dl*-3-phenylpentan-2-one already described.

Action of Phenylmagnesium Bromide on r-*Tropic Acid.*—*r*-Tropic acid (3·5 g.) was added gradually to the Grignard reagent prepared from bromobenzene (13 g.). Two days at the ordinary temperature; decomposition with ice and dilute sulphuric acid. After 3 days at the ordinary temperature, the ethereal layer was separated and dried. The oil obtained was triturated with light petroleum. When the resulting solid was crystallised from benzene, *r*-tropic acid (2·3 g.), m. p. 117—118°, was recovered.

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