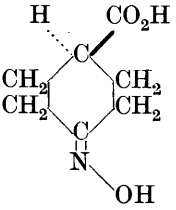
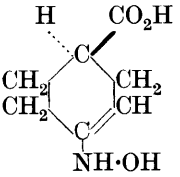
# LXXIII.—*The Configuration of the Doubly-linked Tervalent Nitrogen Atom. Part IV. The Resolution of β-Methyltrimethylene Dithiolcarbonate Carboxyphenylhydrazone.*

By WILLIAM HOBSON MILLS and BERNARD CHARLES SAUNDERS.

THE oxime of *cyclo*hexanone-4-carboxylic acid (I) was shown by Mills and Bain (J., 1910, **97**, 1866; 1914, **105**, 64) to be capable of existing in optically active forms, and the molecular dissymmetry of this compound, thus demonstrated, was referred to the non-planar disposition of the valencies of the doubly-bound tervalent nitrogen atom in the oximino-group, which had been postulated by Hantzsch and Werner to account for the isomerism of the oximes.

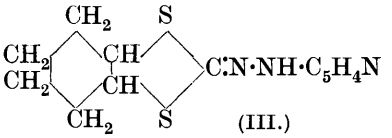
(I.) 

 (II.)

Mills and Bain discussed the possibility of the existence of the oxime in the form (II), which contains an ordinary asymmetric carbon atom, and gave reasons to show that it could not have this formula. It seemed nevertheless desirable to obtain an optically active compound in which the molecular dissymmetry should be similarly dependent on the non-planar distribution of the valencies of a doubly-bound tervalent nitrogen atom, but in which any

uncertainty of constitution arising from a conceivably migratory hydrogen atom should be excluded.

With this object Mills and Schindler (J., 1923, **123**, 312) prepared and investigated the pyridylhydrazone of *cyclo*hexylene dithiolcarbonate (III).




(III.)

They showed that this substance could be resolved into optically active antimerides and concluded that its molecular dissymmetry was to be referred to the non-planar distribution of the valencies of the doubly-linked tervalent nitrogen atom.

This conclusion was based on the assumption that in a dicyclic compound in which a six-ring was fused with a five-ring the *cis*-form would be so much more stable than the *trans*-form that, if one form only was isolable, this would necessarily be the *cis*-form.

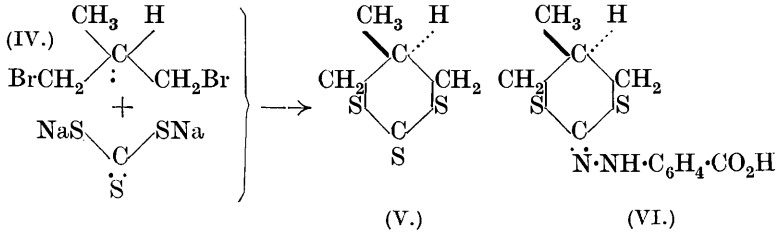
Whilst this assumption was in accordance with previous observations, such as those of Baeyer (*Annalen*, 1890, **258**, 216), on the relative stability of the *cis*- and *trans*-hexahydrophthalic anhydrides, the knowledge which has been gained in the last few years respecting the stability and readiness of formation of the *trans*-forms of five-six dicyclic systems makes it questionable whether it can still be regarded as reliable.

Thus Hückel and Friedrich (*Annalen*, 1926, **451**, 132) found that the *trans*-modification of hexahydro-β-hydrindone is not only capable of existence but actually has a smaller heat of combustion than the *cis*-form, and Perkin and Plant showed (J., 1928, 639) that, by reduction of dihydroquinindene, *cis*- and *trans*-modifications of the hexahydride were obtained in not very disproportionate quantities.

In the absence of definite proof, some doubt must therefore arise as to whether the dicyclic system contained in the pyridylhydrazone investigated by Mills and Schindler has the *cis*- or the *trans*-configuration, and if it has the latter configuration, then the dicyclic system would itself be dissymmetric.

The substance was thus not well suited for the purpose which we had in view. We have therefore undertaken the preparation of a doubly-linked tervalent nitrogen compound which would be better fitted to provide definite evidence of the non-planar distribution of the valencies of the nitrogen atom in this state of combination.

The compound chosen was the o-*carboxyphenylhydrazone* of β-methyltrimethylene dithiolcarbonate (VI).



(IV.) (V.) (VI.)

The starting point in its preparation was methyltrimethylene dibromide (IV), described by Faworsky (*Annalen*, 1907, **354**, 364). This was converted by interaction with sodium trithiocarbonate into the bright yellow β-*methyltrimethylene trithiocarbonate* (V). When this cyclic thiocarbonate was heated with *methyl phenylhydrazine*-o-*carboxylate*, condensation took place with the elimination of the sulphur of the >C:S group as hydrogen sulphide and the formation of the colourless *methyl* ester of the acid (VI), from which the acid itself was obtained by alkaline hydrolysis.

It was found that this acid could be resolved into two antimeric forms with quinine, the resolution being effected with this alkaloid with exceptional ease : when equivalent quantities of the inactive acid and quinine are mixed in alcoholic solution the quinine *d*-acid salt is deposited almost free from its diastereoisomeride. The specific rotation $[\alpha]^{17°}_{5461}$ of the *d*-acid in chloroform was + 12·4° : as sodium salt in dilute sodium hydroxide solution it was + 10·6°.

The acid recovered from the alcoholic mother-liquors of the quinine *d*-acid salt gave, on recrystallisation, the pure *l*-acid. It showed in chloroform the specific rotation $[\alpha]^{17°}_{5461}$ — 12·8°.

The optical activity of this thiocarbonate carboxyphenylhydrazone possesses very considerable stability. Solutions in chloroform usually retained their optical activity undiminished, so far as could be observed, for several days, but after a longer or shorter induction period the rotatory power began to disappear. In one case, however (a chloroform solution of the *l*-acid), no induction period was noticed ; the activity began to disappear at once, falling off in accordance with the unimolecular law with a time of half-change of 3·1 days.

The persistence of the optical activity was also examined in alkaline and in acid media. A solution of the sodium salt in *N*/10-sodium hydroxide, after boiling for ½ hour, showed no perceptible loss of activity, but after 8 hours' boiling the activity had almost entirely vanished. A solution in glacial acetic acid retained its activity

unchanged for several hours at 17°, but lost it completely after the solution had been boiled for ½ hour. We assured ourselves, by recovering the inactive acid from these solutions, that the loss of activity observed was actually due to racemisation and not to more deep-seated changes.

The compound thus clearly possesses molecular dissymmetry. It is desirable, then, to consider its constitution more closely in order to see what conclusions we are justified in drawing from this fact. In view of its method of preparation there might be some doubt as to the structure of the cyclic trithiocarbonate (V). The methyltrimethylene bromide from which it was prepared was obtained by Faworsky's method from *iso*butylene bromide. This method consists in heating the bromide to 205—220°; an equilibrium mixture is then formed,

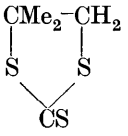
$$(CH_3)_2CBr{\cdot}CH_2Br \rightleftharpoons CH_2Br{\cdot}CH(CH_3){\cdot}CH_2Br$$

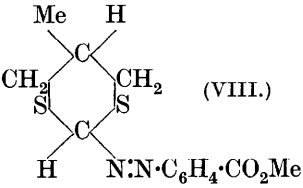
from which the methyltrimethylene bromide is isolated, as the higher fraction, by distillation. Its constitution was established by Faworsky by conversion, through the corresponding glycol, into methylmalonic acid, but the yield obtained of the latter substance was not good.

$$CHMe(CH_2Br)_2 \longrightarrow CHMe(CH_2{\cdot}OH)_2 \longrightarrow CHMe(CO_2H)_2$$

The only alternative to the formula (V) for the cyclic thiocarbonate (which, from its method of preparation, must be a derivative of *iso*butane) would therefore be (VII) * and it could only have this

(VII.)




(VIII.)

formula if the higher fraction were a constant-boiling mixture of the two dibromides and the *iso*butylene bromide were the more readily convertible of the two isomerides into a crystalline trithiocarbonate. Apart from the improbability of two isomeric dibromides forming a constant-boiling mixture, we found that whereas this higher di-

* The possibility of the substance being the third cyclic trithiocarbonate derivable from *iso*butane, $(CH_3)_2CH{\cdot}CH\langle{}^{S}_{S}\rangle CS$, may safely be neglected, since (i) Faworsky (*loc. cit.*) could get no definite evidence of the presence of the corresponding dibromide in the equilibrated mixture and (ii) there is no evidence that such four-ring trithiocarbonates can be prepared; experiments which we made to obtain a compound of this type from ethylidene chloride and sodium trithiocarbonate gave negative results.

bromide fraction gives almost as good a yield (50%) of cyclic trithiocarbonate as pure trimethylene bromide does of trimethylene trithiocarbonate (60%), *iso*butylene bromide under the same conditions gives no corresponding crystalline product, doubtless on account of the tendency of the tertiary bromine to be eliminated as hydrogen bromide instead of being replaced.

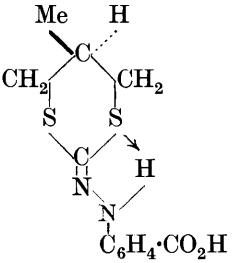
The cyclic trithiocarbonate must therefore be derived from methyltrimethylene bromide and must have the structure (V), and the constantly distilling higher fraction obtainable from the equilibrated dibromides can contain very little, if any, *iso*butylene bromide. It is further to be noted that a hydrazone derived from (VII) would not be dissymmetric.

The condensation product of this trithiocarbonate with methyl phenylhydrazine-*o*-carboxylate, formed with elimination of hydrogen sulphide, has a potentially mobile hydrogen atom and might conceivably be, not the hydrazone (VI), but the azo-compound (VIII). It cannot, however, in fact have the latter structure, since compounds of this type must be coloured, and certainly could not possess persistent molecular dissymmetry. Yet both the ester, and the optically active salts of the corresponding acid are colourless. There would therefore appear to be no escape from the conclusion that these optically active salts are salts of the *o*-carboxyphenylhydrazone of β-methyltrimethylene dithiolcarbonate, and that their molecular dissymmetry is dependent on the non-planar disposition of the valencies of the doubly-linked tervalent nitrogen atom. Their optical activity therefore constitutes a proof that the three valencies of the nitrogen atom in this state of combination do not lie in one plane.

The acid, however, differs from its salts and esters in being bright yellow. It therefore presumably does not correspond exactly with them in constitution. The " acid " is doubtless an internal ammonium salt, $CHMe<(CH_2\cdot S)_2>C\therefore N\cdot \overset{+}{N}H_2\cdot C_6H_4\cdot \overset{-}{C}O_2$, but whether further differences of constitution exist between the acid and its salts and esters, it is difficult to say. The molecular rotations of the coloured acid and the colourless salts are so similar that it would appear that any differences that there may be between them in constitution must be such as do not closely concern the main factors determining the dissymmetry of the molecule.

The optical stability of the compound is remarkable in view of the rapidity with which the oxime, the semicarbazone, and the methylphenylhydrazone of *cyclo*hexanone-4-carboxylic acid undergo racemisation. This stability therefore gives some reason for thinking that the hydrogen atom of the NH group may be co-ordinated

with one of the sulphur atoms, as indicated in formula (IX), in a manner similar to that in which, as has been shown by Sidgwick and




(IX.)

his co-workers (J., 1924, **125**, 532; 1930, 2027), the hydroxylic hydrogen in certain phenols becomes co-ordinated with the oxygen in an *ortho*-situated nitro-, aldehydo-, or carbomethoxy-group.

The non-planar disposition of the valencies of the doubly-linked nitrogen atom would bring this hydrogen atom into a position which would conduce to such co-ordination, and a link of this kind, in spite of its relative weakness, would evidently lead to increased optical stability.

The sulphur atom in becoming thus 3-co-ordinate would acquire asymmetry, but the associated optical activity, dependent in this way on co-ordinated hydrogen, would evidently be excessively unstable. Since, however, the two equilibrium positions of the hydrogen would be unequally favoured on account of their different relations to the methyl group, such an unstable centre of asymmetry might nevertheless permanently contribute a given fraction of the observed rotation. It must, however, be emphasised that, if such a co-ordinate link exists, it must necessarily be extremely weak and its existence would be determined by, but could not determine, the displacement of this group $\cdot NH\cdot C_6H_4\cdot CO_2H$ from the median plane of the cyclic residue $CHMe(CH_2S)_2C{:}N\cdot$ on which the dissymmetry of the molecule must depend.

This displacement, which is to be inferred from the optical activity of the compound, must be primarily due to the non-planar disposition of the valencies of the doubly linked tervalent nitrogen atom.

## EXPERIMENTAL.

β-*Methyltrimethylene Trithiocarbonate* (V).—Sodium (2·3 g.) was dissolved in absolute alcohol (50 c.c.), and dry hydrogen sulphide passed through the solution until this was saturated. Carbon disulphide (5 g.) was added and the solution was then boiled for ½ hour and cooled after dilution with absolute alcohol (50 c.c.); β-methyltrimethylene dibromide (10·8 g.) (Faworsky, *loc. cit.*) was

then added, and the mixture left for 24 hours. The bright yellow solution was poured into a large volume of water and extracted with ether, and the extract dried with calcium chloride. The yellow oil left on evaporation of the ether was dissolved in hot alcohol. On cooling, fine yellow silky needles of the cyclic *ester* were deposited, m. p. after further recrystallisation 74°. Yield, 50% (Found: C, 36·8; H, 5·1; S, 58·6. $C_5H_8S_3$ requires C, 36·6; H, 4·9; S, 58·5%).

β-*Methyltrimethylene Dithiolcarbonate Phenylhydrazone.*—The trithiocarbonate (1·64 g.) was boiled with an alcoholic solution of phenylhydrazine (3·8 g.) for 3 hours, during which time hydrogen sulphide was copiously evolved. On cooling, crystals of the *phenylhydrazone* were deposited as glistening plates (1 g.), m. p. 89° after recrystallisation from alcohol (Found: C, 55·7; H, 6·1; N, 12·0; S, 27·1. $C_{11}H_{14}N_2S_2$ requires C, 55·5; H, 5·9; N, 11·8; S, 26·9%).

*Methyl Phenylhydrazine*-o-*carboxylate.*—This compound, which has not been previously described, was prepared by a method worked out by one of us and A. Belchetz. Methyl anthranilate (25 g.) was diazotised by addition of water (100 c.c.), concentrated hydrochloric acid (39 c.c.), and then sodium nitrite (11 g.) in water (20 c.c.). The resulting solution was added to sodium sulphite heptahydrate (80 g.) and hydrated sodium carbonate (112 g.) in water (100 c.c.) at 0° and stirred at room temperature for 3 hours. The temperature of the red solution was raised to 30°, sulphur dioxide was led in for 30 minutes, the temperature was raised to 70°, and the solution was filtered, cooled, and treated with concentrated hydrochloric acid (120 c.c.); the ester hydrochloride then gradually crystallised together with a certain amount of the hydrochloride of the hydrazino-acid. This mixture was collected, chloroform (250 c.c.) and water (10 c.c.) were added and then sodium bicarbonate introduced gradually, with vigorous shaking, till no more effervescence occurred. The residue obtained by evaporation of the chloroform, recrystallised from light petroleum (b. p. 40—60°), gave the pure *ester*, m. p. 48° (Found: C, 57·9; H, 6·2; N, 17·0. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0; N, 16·9%).

o-*Carbomethoxyphenylhydrazone of* β-*Methyltrimethylene Dithiolcarbonate.*—The trithiocarbonate (3·4 g.) and methyl phenylhydrazine-*o*-carboxylate (2·7 g.; 1 mol.) were boiled together in methylalcoholic solution for 3 hours, during which time hydrogen sulphide was copiously evolved. On cooling, the *hydrazone* crystallised in short, almost colourless needles (3·9 g.). Recrystallised from alcohol, it was obtained in short well-formed needles, m. p. 91·5—93° (Found: C, 52·6; H, 5·3; N, 9·7; S, 21·8. $C_{13}H_{16}O_2N_2S_2$ requires C, 52·7; H, 5·4; N, 9·5; S, 21·6%).

o-*Carboxyphenylhydrazone of* β-*Methyltrimethylene Dithiolcarbonate.*—Sodium (0·20 g.) was dissolved in rectified spirit (20 c.c.), and the carbomethoxyphenylhydrazone (1·2 g.) added. The mixture was boiled for 20 minutes and cooled slightly (if cooled too much the sodium salt crystallises). 50% Hydrochloric acid was added drop by drop until the solution was just acid. On cooling, the *acid* crystallised and on recrystallisation from alcohol gave elongated canary-yellow prisms of the oblique system; m. p. 202°. Yield, quantitative (Found: C, 50·9; H, 5·0; N, 10·1; S, 22·8. $C_{12}H_{14}O_2N_2S_2$ requires C, 51·1; H, 5·0; N, 9·9; S, 22·7%).

*Resolution of the* o-*Carboxyphenylhydrazone of* β-*Methyltrimethylene Dithiolcarbonate.*—The *dl*-carboxyphenylhydrazone (5·64 g.) and quinine hydrate (7·56 g.) were dissolved in hot 90% alcohol (200 c.c.) and the filtered solution was kept; the *quinine* salt separated gradually in fine colourless needles. The weight of dried salt obtained was 6·2—6·7 g., a yield of 52—55%. It melted at 184—185°, and was very soluble in chloroform, slightly in cold alcohol, and practically insoluble in water (Found: C, 63·3; H, 6·4; N, 9·5. $C_{32}H_{38}O_4N_4S_2$ requires C, 63·4; H, 6·3; N, 9·2%).

After recrystallisation from 90% alcohol the salt showed a constant specific rotation. The following readings were made on a chloroform solution ($l = 2$; $c = 1·064$ g./100 c.c.) at 17°: $\alpha_{5461} = -5·44°$; $[\alpha]_{5461} = -255°$; $\alpha_{5780} = -4·60°$; $[\alpha]_{5780} = -216°$.

In chloroform solutions of similar concentration the quinine salt of the *dl*-compound, made by dissolving equivalent quantities of quinine and *dl*-hydrazone, had $[\alpha]^{17°}_{5461} - 300°$ and $[\alpha]^{17°}_{5780} - 242°$.

*The* d-*acid.* The quinine salt (1·546 g.) was dissolved in chloroform (50 c.c.) and the quinine was removed by repeated extraction with dilute sulphuric acid. The greenish-yellow chloroform solution of the acid was examined polarimetrically after adjustment of the volume to 50 c.c. ($l = 4$; $c = 1·439$; $t = 17°$): $\alpha_{5461} = +0·72°$; $[\alpha]_{5461} = +12·5°$.

The acid was recovered from the chloroform solution by addition of light petroleum at 0° and crystallised in fine greenish-yellow needles, m. p. 199°. It was divided into two portions. The first was analysed (Found: C, 50·7; H, 5·0. Calc.: C, 51·1; H, 5·0%). The second was examined polarimetrically ($l = 4$; $c = 1·42$; $t = 17°$): $\alpha_{5461} = +0·70°$; $[\alpha]_{5461} = +12·3°$.

The sodium salt in aqueous solution has a somewhat smaller molecular rotation than the free acid. Quinine salt (0·6825 g.) was dissolved in chloroform (20 c.c.). After removal of the quinine and readjustment of the volume of the chloroform solution to 20 c.c., the solution gave $\alpha^{17°}_{5461} + 0·41°$ ($l = 2$), whence $[\alpha]_{5461} = +12·9°$. The chloroform was then extracted with *N*/5-sodium hydroxide

solution, and the volume of the latter adjusted to 20 c.c. This colourless alkaline solution of the sodium salt had $\alpha_{5461}$ + 0·34°, giving $[\alpha]_{5461}$ + 10·7° calculated as for the acid. The acid recovered from the solution by acidification with dilute sulphuric gave, when dried and dissolved in chloroform, the following data ($l = 2$; $c = 1{\cdot}406$; $t = 17°$): $\alpha_{5461} = + 0{\cdot}35°$; $[\alpha]_{5461} = + 12{\cdot}4°$.

A similar experiment in which the quinine salt was decomposed with $N/5$-sodium hydroxide and chloroform gave for the acid in alkaline solution $[\alpha]_{5461}$ + 10·5°.

On the other hand the piperidine salt has, in chloroform, a considerably higher molecular rotation than the free acid. In an experiment, made to look for possible mutarotation induced by piperidine in chloroform solution, a greenish-yellow solution of the acid ($c = 1{\cdot}44$) showing $\alpha_{5461}$ + 0·74° ($l = 4$), corresponding with $[\alpha]_{5461}$ + 12·8°, gave on addition of a few drops of piperidine a colourless solution showing $\alpha_{5461}$ + 1·30° ($l = 4$), from which the *d*-acid was recovered unchanged after removal of the piperidine with dilute sulphuric acid.

*The* l-*acid*. The alcoholic mother-liquors obtained in the preparation of the quinine salt were mixed with chloroform and the quinine was completely removed by repeated extraction with dilute sulphuric acid. On the addition of light petroleum to the dried greenish-yellow solution the *l*-acid crystallised, m. p. 199° (Found: C, 50·6; H, 5·1. Calc.: C, 51·1; H, 5·0%). A solution in chloroform was examined polarimetrically with the following results ($l = 4$; $c = 1{\cdot}463$; $t = 17°$): $\alpha_{5461} = - 0{\cdot}75°$, whence $[\alpha]_{5461} = - 12{\cdot}8°$.

*Racemisation*. (i) *In chloroform solution*. In this solvent both the *d*- and the *l*-acid usually retained their optical activity unchanged over several days. In one case a solution (50 c.c.) of the *d*-acid (0·5708 g.), after being kept under observation for 3½ hours, was boiled for ½ hour (*), observed, boiled for 1½ hours (**), observed, and then left over-night. The readings were as follows.

| Time (hours). | $\alpha^{17°}_{5461}$. | Time (hours). | $\alpha^{17°}_{5461}$. |
|---|---|---|---|
| 0 | + 0·60° | 4½ | 0·58° |
| 2½ | 0·59 | ** | |
| 3½ | 0·60 | 6½ | 0·59 |
| * | | 7½ | 0·59 |
| | | 24 | 0·01 |

A chloroform solution of the *l*-acid containing 0·439 g. of acid in 30 c.c., on the other hand, began to racemise at once at 17°. The following table shows the rate at which the activity disappeared. It followed very nearly the unimolecular law.

| Time (hours). | $\alpha_{5461}^{17°}$. | $1/t \cdot \log_{10} a_0/a_t$. ($t$ in days) | Time (hours). | $\alpha_{5461}^{17°}$. | $1/t \cdot \log_{10} a_0/a_t$. |
|---|---|---|---|---|---|
| 0 | − 0·75° | — | 72 | − 0·39° | 0·095 |
| 24 | − 0·60 | 0·097 | 96 | − 0·31 | 0·096 |
| 48 | − 0·48 | 0·092 | 144 | − 0·19 | 0·099 |

(ii) *In glacial acetic acid.* A solution (20 c.c.) of the *d*-acid (0·1815 g.) in glacial acetic acid showed $\alpha_{5461}^{17°}$ + 0·18° ($l$ = 2). This rotation remained unchanged for several hours. The solution was then boiled for ½ hour, re-examined, and found to be optically inactive. The substance recovered from the solution proved to be the pure inactive acid, m. p. 201—202°.

(iii) *In dilute alkali.* A solution (25 c.c.) of *d*-acid (0·381 g.) in *N*/5-sodium hydroxide solution showed $\alpha_{5461}^{17°}$ + 0·23° and retained this value for several days. After ½ hour's boiling the rotation was the same. After being boiled for 8 hours, the solution had lost most of its activity ($\alpha_{5461}$ + 0·02°). On acidification with dilute sulphuric acid the pure inactive acid, m. p. 201—202°, was precipitated.

*Trimethylene Dithiolcarbonate* o-*Carbomethoxyphenylhydrazone.*—This and the following compound were prepared in order to gain experience in the methods to be followed in obtaining the corresponding β-methyltrimethylene derivatives.

*Trimethylene trithiocarbonate*, m. p. 80° (Found : S, 64·4. $C_4H_6S_3$ requires S, 64·0%), was prepared in a yield of over 60% by the method described for the β-methyltrimethylene compound. When this substance (0·38 g.) and methyl phenylhydrazine-*o*-carboxylate (0·34 g.) were boiled together in methyl-alcoholic solution for 3 hours, hydrogen sulphide was evolved. The *hydrazone*, which crystallised on cooling, formed almost colourless needles, m. p. 139—140°, from methyl alcohol (Found : C, 50·8; H, 5·0; S, 22·8. $C_{12}H_{14}O_2N_2S_2$ requires C, 51·1; H, 5·0; S, 22·7%).

*Trimethylene dithiolcarbonate* o-*carboxyphenylhydrazone.* The ester (1·5 g.) was boiled for ½ hour with a solution of sodium (0·3 g.) in rectified spirit (20 c.c.). The mixture, acidified with dilute hydrochloric acid, deposited the *carboxy-hydrazone*, which formed long canary-yellow needles, m. p. 212°, from alcohol (Found : C, 49·2; H, 4·6; S, 24·0. $C_{11}H_{12}O_2N_2S_2$ requires C, 49·3; H, 4·5; S, 23·9%). The acid dissolves, rather slowly, in aqueous sodium bicarbonate, giving a colourless solution of the sodium salt.

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