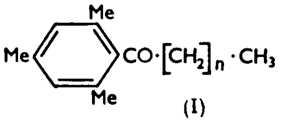
394. *The Formation of Oxothiomorpholides in the Willgerodt Reaction.*

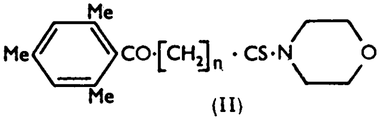
By P. A. Barrett.

From the Willgerodt reaction (sulphur–morpholine) with acetophenone, propiophenone, and their *p*-dimethylamino-derivatives the α-oxo-ω-thiomorpholides (VI), (XI), (XIV), and (XV) have been isolated, in addition to the orthodox Willgerodt thiomorpholides (V), (X), and (XIII). The formation of the oxothiomorpholides is favoured by the addition of nitrobenzene and suppressed by the presence of excess of hydrogen sulphide. They are however not appreciably reduced by hydrogen sulphide to the thiomorpholides, and are thus not shown to be intermediate in the formation of the latter. Their isolation does not necessitate revision of current theories on the mechanism of the Willgerodt reaction.

Dauben and Rogan[1] reported the isolation of the oxothiomorpholides (II; $n = 0$—2) on Willgerodt reaction with the mesityl ketones (I). They attributed formation of this new type of product to the weakly ketonic nature of mesityl ketones. Independently, we had isolated analogous oxothiomorpholides and shown that their formation is not limited to abnormal ketones.

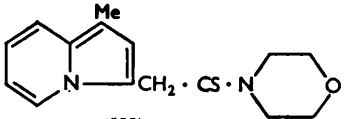


(I)

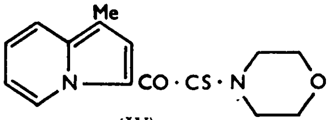


(II)

Our work had its origin in a Willgerodt reaction with 3-acetyl-1-methylpyrrocoline, from which was isolated in low yield, the orthodox product (III), and a compound to which on the basis of analysis and ultraviolet spectrum is assigned the constitution (IV). The method was therefore of little promise as a route to pyrrocolylacetic acids, but the isolation of the substituted thioglyoxylamide (IV), of a type then unknown as a product of Willgerodt reactions, suggested an examination of the behaviour of *p*-dimethylaminoacetophenone since reactivity of the 3-position in the pyrrocoline ring is similar to that of the *p*-position in dimethylaniline. Three compounds (V), (VI), and (VII) were then isolated. *p*-Dimethylaminophenylacet-thiomorpholide (V) was easily separated, through its greater basicity, from the scarlet mixture of (VI) and (VII), which formed mixed crystals but was separated by chromatography on alumina into yellow *p*-dimethylaminophenylglyoxylthiomorpholide (VI) and the intensely red *p*-dimethylaminophenyldithioglyoxylmorpholide (VII). The constitution of the product (VI) is confirmed by hydrolysis to *p*-dimethylaminophenylglyoxylic acid and by desulphurisation with silver acetate to *p*-dimethylaminophenylglyoxylmorpholide (VIII). The alternative structure (IX), not rigidly excluded by this evidence, is not only improbable on mechanistic grounds but is excluded by the ultraviolet absorption spectrum, discussed below. The constitution of the dithio-compound (VII) is confirmed by formation of this compound from the monothioanalogue (VI) by phosphorus pentasulphide. Re-examination of the Willgerodt reaction with acetophenone showed that the formation of oxothioamides is not abnormal. In addition to phenylacet-thiomorpholide[2] (X), there was isolated phenylglyoxylthiomorpholide (XI) which was shown (ultraviolet spectrum) to comprise 20% of the reaction



(III)



(IV)

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[1] Dauben and Rogan, *J. Amer. Chem. Soc.*, 1956, **78**, 4135.

[2] Schwenk and Bloch, *ibid.*, 1942, **64**, 3051.

product: its constitution was confirmed by desulphurisation to phenylglyoxylmorpholide (XII), but its alkaline hydrolysis gave only mandelic acid. Lacking the tertiary amino-group, these products (X) and (XI) were not separable by the method used previously but differential hydrolysis with concentrated hydrochloric acid was a satisfactory method for the isolation of the oxo-amide (XI). The oxothiomorpholides (VI) and (XI) might have been intermediates in the formation of the thiomorpholides; in agreement, yields of

$$p\text{-R}\cdot C_6H_4\cdot CH_2\cdot CS\cdot N{<}[CH_2\cdot CH_2]_2{>}O$$

(V): $R = NMe_2$
(X): $R = H$

$$p\text{-R}\cdot C_6H_4\cdot CO\cdot CS\cdot N{<}[CH_2\cdot CH_2]_2{>}O$$

(VI): $R = NMe_2$
(XI): $R = H$

(VII) $p\text{-}Me_2N\cdot C_6H_4\cdot CS\cdot CS\cdot N{<}[CH_2\cdot CH_2]_2{>}O$

$$p\text{-R}\cdot C_6H_4\cdot CO\cdot CO\cdot N{<}[CH_2\cdot CH_2]_2{>}O$$

(VIII): $R = NMe_2$
(XII): $R = H$

$$p\text{-}Me_2N\cdot C_6H_4\cdot CS\cdot CO\cdot N{<}[CH_2\cdot CH_2]_2{>}O$$

(IX)

the former were increased by the addition of an oxidising agent (nitrobenzene) to the reaction mixture (though they were not then the sole products), and were reduced virtually to zero when the reaction was carried out in a continuous current of hydrogen sulphide. That oxothioamides have not previously been isolated from Willgerodt reactions is probably related to variations in the reaction conditions used. The deficiency of hydrogen sulphide which favours their formation is more likely to be encountered in the sulphur–morpholine variant,[2] carried out in open vessels, than in the earlier methods[3] carried out under pressure.

p-Dimethylaminopropiophenone with sulphur and morpholine also gave two main products (XIII) and (XIV), with smaller amounts of *p*-dimethylaminocinnamthiomorpholide, and an unidentified compound $C_{11}H_{11}NS_3$. No analogue of the dithio-compound (VII) was isolated. The yield of the oxo-amide (XIV) was increased and no amide (XIII) could be isolated when nitrobenzene was added to the reaction mixture. The yield of the latter product (XIII) was increased and that of the former reduced by working in an atmosphere of hydrogen sulphide, but the course of the reaction was less completely influenced than in the case of the acetophenones.

$$p\text{-R}\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CS\cdot N{<}[CH_2\cdot CH_2]_2{>}O$$

(XIII): $R = NMe_2$
(XVI): $R = H$

$$p\text{-R}\cdot C_6H_4\cdot CO\cdot CH_2\cdot CS\cdot N{<}[CH_2\cdot CH_2]_2{>}O$$

(XIV): $R = NMe_2$
(XV): $R = H$

The reaction of propiophenone with sulphur and morpholine has been used[4, 5] for the preparation of β-phenylpropionic acid by hydrolysis of the total reaction product, but the intermediate thiomorpholide (XVI) has not been described. From the reaction was isolated in small yield a compound shown by analysis and ultraviolet spectrum to have the constitution (XV), but none could be isolated on reaction in the presence of nitrobenzene. The orthodox Willgerodt product (XVI) has not been isolated.

p-Dimethylaminobutyrophenone with sulphur and morpholine in the presence of nitrobenzene gave a compound (XVII). Its hypothetical thiomorpholide precursor presumably suffered hydrolysis during the working up.[6]

$$p\text{-}NMe_2\cdot C_6H_4\cdot CO\cdot CH_2\cdot CH_2\cdot CO\cdot N{<}[CH_2\cdot CH_2]_2{>}O$$

(XVII)

Although the formation of the oxothiomorpholides (VI), (XI), and (XIV) is substantially suppressed by excess of hydrogen sulphide, the oxothiomorpholides are not

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[3] For refs. see Carmack and Spielman in "Organic Reactions," Vol. III, Chapman and Hall, London, 1946, p. 83.

[4] Schwenk and Papa, *J. Org. Chem.*, 1946, **11**, 798.

[5] McMillan and King, *J. Amer. Chem. Soc.*, 1948, **70**, 4148.

[6] Cf. Bernthsen, *Annalen*, 1877, **184**, 297.

themselves reduced by hydrogen sulphide in morpholine, but are recovered substantially unchanged. When heated in morpholine with sulphur and hydrogen sulphide, however, some reduction to the thiomorpholides occurs. An explanation of this difference in behaviour is suggested by the properties of the dithio-oxomorpholide (VII). This compound, unlike the accompanying oxothiomorpholide (VI), was rapidly converted by hydrogen sulphide into the thiomorpholide (V) [this is the preferred method for freeing the oxothiomorpholide (VI) from dithio-compound (VII)]. It is suggested that in the presence of sulphur the oxothiomorpholide (VI) slowly gives the thiomorpholide (V), *via* the dithio-compound (VII). The conversion of the oxothiomorpholides (VI), (XI), and (XIV) into the thiomorpholides (V), (X), and (XIII) by sulphur and hydrogen sulphide is however not sufficiently rapid for this to be the route by which the very high proportion of thiomorpholides is formed in Willgerodt reactions carried out in the presence of hydrogen sulphide. Unless the reaction of the oxothiomorpholides with sulphur and hydrogen sulphide in morpholine does not adequately reproduce the reducing conditions of the reaction mixture, isolation of the former does not afford evidence on the formation of the thiomorpholides, *i.e.*, on the mechanism of the Willgerodt reaction.

Ultraviolet Absorption Spectra (with Dr. A. J. EVERETT).—The ultraviolet absorption maxima of the compounds prepared are collected in the Table. The spectrum of phenylacet-thiomorpholide (X) shows a single sharp peak at 282 mμ with rising end-absorption below 240 mμ, the absorption falling sharply to zero below 350 mμ; the spectrum is almost identical with that of acet-thiomorpholide [7] which has $\lambda_{max.}$ 278 mμ; it differs from the curve given by Dauben and Rogan [1] in lacking the shoulder at 365 mμ. This shoulder is however a feature of the spectrum of phenylglyoxylthiomorpholide (XI), which shows a

Ultraviolet absorption spectra of thiomorpholides and related compounds.

	$\lambda_{max.}$ (mμ)	ε
Acet-thiomorpholide	278	15,900
Dimethyl-*p*-toluidine [a]	255, 303	34,700 2,240
Phenylacet-thiomorpholide (X)	282	15,650
p-Dimethylaminophenylacet-thiomorpholide (V)	264, 279, 305 *	20,900, 19,100, 3,750
β-(*p*-Dimethylaminophenyl)propionthiomorpholide (XIII)	262, 279, 314 *	18,600, 17,700, 1,950
Acetophenone [b]	240, 278,† 320 †	13,000 1,100, 50
Phenylglyoxylthiomorpholide (XI)	254, 269, 376—384	17,850, 17,300, 1,020
Benzoylacet-thiomorpholide (XV)	244, 282, 320	11,350, 13,500, 6,530
Phenylglyoxylmorpholide (XII)	253, 285 *	14,000, 2,600
p-Dimethylaminoacetophenone	239, 334	6,600, 27,000
p-Dimethylaminophenylglyoxylthiomorpholide (VI)	264, 354	14,170, 27,000
p-Dimethylaminobenzoylacet-thiomorpholide (XIV)	243, 283, 340	7,120, 15,590, 27,400
β-(*p*-Dimethylaminobenzoyl)propionmorpholide (XVII)	237, 330	8,200, 33,300
p-Dimethylaminophenylglyoxylmorpholide (VIII)	243, 350	6,500, 28,700
p-Dimethylaminophenyldithioglyoxylmorpholide (VII)	246, 272, 458	8,550, 20,500, 47,700
Oxaldithiomorpholide	276	18,000
1-Methylpyrrocoline [c]	239, 280, 288, 300, 360	33,000, 2,120, 3,150, 4,350, 2,000
(1-Methyl-3-pyrrocolyl)acet-thiomorpholide (III)	241, 281, 358—366	38,000, 18,000, 2,300
3-Acetyl-1-methylpyrrocoline	225, 229, 265, 370, 382	14,600, 13,100, 24,000, 15,600, 14,300
(1-Methyl-3-pyrrocolyl)glyoxylthiomorpholide (IV)	220, 227, 265, 398	12,500, 11,900, 25,000, 20,000
p-Dimethylaminocinnamthiomorpholide	236, 288—322,† 380	11,850, 18,750, 8,000
Substance $C_{11}H_{11}NS_3$	265, 325, 451	19,200, 6,300, 39,700

* Inflexion. † Fine structure.

[a] Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838. [b] Braude, *Ann. Reports*, 1945, **42**, 105.
[c] Barrett, unpublished work.

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[7] Peak and Stansfield, *J.*, 1952, 4067.

broad peak at 360—385 mμ (ε 1020)—Dauben and Rogan's sample was probably contaminated with 20% of phenylglyoxylthiomorpholide. The spectra of dimethylaminophenyl-acet- and -propion-thiomorpholides (V and XIII) are almost identical, showing a broad double peak at 264 and 279 mμ, of which the former is attributed to the chromophore of dimethyl-*p*-toluidine and the latter to that of acet-thiomorpholide.

The spectra of α-(*p*-dimethylaminobenzoyl)acet-thiomorpholide (XIV) and β-(*p*-dimethylaminobenzoyl)propionmorpholide (XVII) agree in showing the two peaks at 240 and 340 mμ referable to *p*-dimethylaminoacetophenone. The former shows also the acet-thiomorpholide peak. The spectrum of benzoylacet-thiomorpholide (XV) shows a peak at 244 mμ referable to acetophenone, acet-thiomorpholide absorption at 282 mμ, and a shoulder at 320—322 mμ (ε 6530) which cannot be convincingly referred to either of these chromophores.

The substituted glyoxylthiomorpholides (IV), (VI), and (XI) are formally conjugated, and their spectra would not be expected to admit of the same clear interpretation in terms of constituent chromophores as the compounds considered above. However it appears that interaction between the groups is not sufficiently great to destroy the integrity of the absorption maxima associated with the individual chromophores, which survive, though in some cases with considerable alteration in wavelength. This is most clearly seen in the pyrrocolyl example (IV), whose spectrum very closely resembles that of the corresponding 3-acetylpyrrocoline except that the absorption maximum at 265 mμ is broadened towards 280 mμ, which is interpreted as a contribution from the thiomorpholide chromophore. Phenylglyoxylthiomorpholide (XI) shows a broad double peak at 254 and 269 mμ, of which the latter may represent the thiomorpholide chromophore, and the former peak together with the shoulder mentioned above, may be referred to the acetophenone chromophore, both contributions having suffered considerable modification. The dimethylamino-analogue (VI) shows a survival of two absorption maxima, of which that at 264 mμ may represent a fusion of the shorter-wavelength acetophenone peak with the thiomorpholide contribution, and that at 354 mμ may be referred to dimethylaminoacetophenone. The spectra of phenylglyoxylmorpholide (XII) and its dimethylamino-analogue (VIII) are less confused. The morpholide group appears to show neither contribution to, nor influence on, the spectra, which respectively resemble rather closely those of acetophenone and dimethylaminoacetophenone. Similarly the spectrum of oxaldithiomorpholide [8] shows no evidence of interaction between the two thioamide groups, the maximum being identical with that of, *e.g.*, acet-thiomorpholide.

A similar absence of interaction being assumed for the dithioglyoxylmorpholide (VII), its absorption maximum at 272 mμ (ε 20,500) is attributed to the thiomorpholide chromophore, and the maxima at 246 and 458 mμ are referred to the dimethylaminothioacetophenone chromophore. The absence of the 458 mμ maximum from the spectra of the monothioglyoxylmorpholides (*e.g.*, VI and XI) shows that the sulphur atom is always in the β- and not the α-position.

EXPERIMENTAL

Ultraviolet absorption spectra were measured in ethanol in a Hilger "Uvispek" spectrophotometer.

Willgerodt Reactions.—(a) 3-*Acetyl*-1-*methylpyrrocoline.* A mixture of 3-acetyl-1-methylpyrrocoline [9] (18 g.), sulphur (5·5 g.), and morpholine (15 ml.) was boiled under reflux for 21 hr., then extracted with boiling ether (1·5 l. in portions). The extracts were decanted from tar, and the ether removed. The oil was washed with water to remove morpholine and the residual semisolid material was crystallised from ethanol, to give (1-*methyl*-3-*pyrrocolyl*)*glyoxylthiomorpholide* (IV) (2·5 g.), as orange needles, m. p. 192° (Found: C, 62·6; H, 5·6; O, 11·5; N, 9·3; S, 10·6. $C_{15}H_{16}O_2N_2S$ requires C, 62·5; H, 5·6; O, 11·1; N, 9·7; S, 11·1%). (It is

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[8] King and McMillan, *J. Amer. Chem. Soc.*, 1947, **69**, 1207.

[9] B.P. Appl. 35,513/1953.

probable that much of this material was discarded in the ether-insoluble tar.) The mother-liquors were evaporated to give semisolid material from which by crystallisation from light petroleum (b. p. 60—80°), in which the glyoxylthiomorpholide is sparingly soluble, was isolated (*1-methyl-3-pyrrocolyl)acet-thiomorpholide* (III) (0·6 g.) as cream-coloured needles, m. p. 130° (Found: C, 65·7; H, 6·4; O, 6·2; N, 9·5; S, 11·8. $C_{15}H_{18}ON_2S$ requires C, 65·7; H, 6·6; O, 5·8; N, 10·2; S, 11·7%).

(b) *Acetophenone.* (i) Following Schwenk and Bloch,[9] acetophenone (12 ml.), sulphur (4·8 g.), and morpholine (9·0 ml.) were boiled under reflux for 8 hr. On cooling, the mixture deposited crystals which were lixiviated with water, and the solid (12 g.) was filtered off and recrystallised several times from ethanol to give phenylacet-thiomorpholide (X), colourless prisms (7·5 g., 34%), m. p. 79—80° (Schwenk and Bloch[9] give m. p. 79—80°). From the filtrate, by evaporation, was obtained a mixture of colourless and yellow crystals from which by hand-picking of the yellow and recrystallisation from ethanol was obtained a small sample of phenylglyoxylthiomorpholide (XI), m. p. 113°, not depressed on admixture with material prepared as described below.

The total product from a second experiment, after one crystallisation from ethanol (10 g.), was shown by a comparison of its ultraviolet spectrum with that of the pure components to contain 20·8% of the glyoxylthiomorpholide.

(ii) With addition of nitrobenzene. Acetophenone (120 ml.), sulphur (48 g.), morpholine (180 ml.), and nitrobenzene (120 ml.) were boiled under reflux for 4 hr. The product was washed free from morpholine by water (3 × 1 l.), and the oil steam-distilled. The aqueous layer was poured off and to the semisolid residue was added a mixture of concentrated hydrochloric acid (630 ml.) and acetic acid (630 ml.). The mixture was boiled under reflux for 2 hr., poured on ice, and basified by aqueous ammonia. The solid was filtered off, washed with water, dried *in vacuo*, and recrystallised from ethanol to give *phenylglyoxylthiomorpholide* (XI) (65 g., 28%) as yellow plates, m. p. 114° (Found: C, 61·4; H, 5·4; O, 14·5; S, 13·7. $C_{12}H_{13}O_2NS$ requires C, 61·4; H, 5·5; O, 13·6; S, 13·6%).

(iii) In presence of excess of hydrogen sulphide. Acetophenone (48 ml.), sulphur (19·2 g.), and morpholine (54 ml.) were boiled under reflux for 4 hr. in a current of hydrogen sulphide. Working up as described under (i) gave phenylacet-thiomorpholide (67 g., 76%). From the residue obtained by evaporation of the filtrates from the crystallisations there was obtained, by the hydrolysis method described under (ii), phenylglyoxylthiomorpholide (2·5 g.), m. p. 112—113°.

(c) p-*Dimethylaminoacetophenone.* (i) *p*-Dimethylaminoacetophenone[10] (32·6 g.), sulphur (9·6 g.), and morpholine (26·0 ml.) were boiled under reflux for 4 hr. The product solidified on cooling. It was recrystallised from ethanol to give solid (38 g.). This was dissolved in warm acetic acid (175 ml.), the solution filtered, and diluted with water (200 ml.). Scarlet crystals rapidly separated and after ½ hr. were filtered off, washed with a little 50% aqueous acetic acid and then with water, and crystallised from ethanol, to give a mixture of the mono- and di-thioglyoxylmorpholide (VI and VII) as red plates (8·3 g.), m. p. 159—162° (Found: C, 59·3; H, 6·0; S, 13·8%). The aqueous acetic acid filtrate was basified with ammonia solution with cooling. The precipitated, almost colourless, solid was filtered off, washed with water, and recrystallised from ethanol, to give p-*dimethylaminophenylacet-thiomorpholide* (V) (25·2 g.) as colourless, serrated prisms, m. p. 140—142° (Found: C, 64·0; H, 7·2; O, 6·4; N, 10·3; S, 11·9. $C_{14}H_{20}ON_2S$ requires C, 63·6; H, 7·6; O, 6·1; N, 10·6; S, 12·1%). 5 g. of mixed mono- and di-thioglyoxylmorpholides were dissolved in benzene (50 ml.) and adsorbed on alumina (450 g.; 4 × 40 cm.). Elution with benzene developed an orange head band and a yellow tail band without effecting their complete separation. The orange band was eluted and adsorbed on a second column. Development gave discrete orange and yellow bands. The orange band was eluted, and after removal of the solvent gave deep crimson solid. Crystallisation from ethanol gave p-*dimethylaminophenyldithioglyoxylmorpholide* (VII) (0·5 g.), deep red needles with a metallic reflex, m. p. 200° (Found: C, 57·6; H, 6·3; N, 9·5; S, 21·4. $C_{14}H_{18}ON_2S_2$ requires C, 57·1; H, 6·1; N, 9·5; S, 21·8%). The yellow bands were stripped with chloroform and the eluate on evaporation and crystallisation from ethanol gave *p*-dimethylaminophenylglyoxylthiomorpholide (see below) (2·2 g.; m. p. 153—154°) contaminated with low-melting material presumably formed by decomposition on the column. For the preparation of pure

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[10] Nineham, *J.*, 1952, 635.

monothioglyoxylmorpholide the following method is preferred. Mixed mono- and di-thioglyoxylmorpholides (14·0 g.) (prepared as described above) were boiled under reflux in morpholine (20 ml.) while a current of hydrogen sulphide was passed for 5 min. The product was cooled somewhat and diluted with ethanol (30 ml.). Pale yellow crystalline material separated and was filtered off and dried. Recrystallisation from ethanol gave p-*dimethylaminophenylglyoxylthiomorpholide* (VI) (11·0 g.) as pale yellow prisms, m. p. 161—162° (Found: C, 60·8; H, 6·2; O, 11·6; N, 10·3; S, 11·3. $C_{14}H_{18}O_2N_2S$ requires C, 60·4; H, 6·5; O, 11·5; N, 10·1; S, 11·5%). The filtrates from the crystallisations were taken to dryness and the residue, consisting of a mixture of *p*-dimethylaminophenyl-acet- and -glyoxyl-thiomorpholides, was separated by the acetic acid method described above, to give *p*-dimethylaminophenylacet-thiomorpholide (0·8 g.), m. p. 141—142°.

(ii) With addition of nitrobenzene. *p*-Dimethylaminoacetophenone (163 g.), sulphur (96 g.), morpholine (174 ml.), and nitrobenzene (124 ml.) were boiled under reflux for 4 hr. The product, while still warm, was diluted with an equal volume of ethanol and set aside for 48 hr. The red crystals (251 g.) were filtered off, washed with ethanol, dissolved in glacial acetic acid (2 l.) at *ca.* 80°, the solution filtered from sulphur, and left for 48 hr. The mixed thioglyoxylmorpholides (83 g.) were filtered off and washed with glacial acetic acid. The acid filtrate was diluted with water (2 l.) and left for 6 hr. The second crop of mixed thioglyoxylmorpholides (36 g.) was filtered off and washed with 50% aqueous acetic acid. The aqueous acid filtrate was cautiously basified (ammonia) at 0°. The precipitated solid (106 g.), consisting of *p*-dimethylaminophenylacet-thiomorpholide still containing thioglyoxylmorpholides, was dissolved in glacial acetic acid (400 ml.), diluted with water (500 ml.), and left for 1 hr. The third crop of mixed thioglyoxylmorpholides (10 g.) was filtered off. The combined crops of crude material (129 g.) were crystallised from ethanol (*ca.* 4 l.), to give mixed mono- and di-thio-glyoxylthiomorpholides as red plates (115 g.), m. p. 160—161°. These were boiled under reflux in morpholine (115 ml.) while a current of hydrogen sulphide was passed for 10 min. The solution was cooled somewhat, diluted with an equal volume of ethanol, and left 6 hr. The pale yellow solid was filtered off, washed with ethanol, and dried at 60° (104 g.; m. p. 151—152°). Crystallisation from ethanol gave *p*-dimethylaminophenylglyoxylthiomorpholide (98 g.), m. p. 161—162°.

The second aqueous acetic acid filtrate was worked up as described above, to give *p*-dimethylaminophenylacet-thiomorpholide (38 g.), m. p. 139—140°.

(iii) In the presence of excess of hydrogen sulphide. *p*-Dimethylaminoacetophenone (16·3 g.), sulphur (3·2 g.), and morpholine (18 ml.) were boiled under reflux for 4 hr. while a slow stream of hydrogen sulphide was bubbled through. The mixture was cooled, diluted with a little ethanol, and left overnight. The solid (20 g.) was filtered off, washed with ethanol, and dissolved in water by addition of 2N-hydrochloric acid. The aqueous solution was filtered from sulphur, treated with charcoal (2 g.), refiltered, and basified with ammonia at 0°, and the precipitated solid was filtered off, washed, and dried *in vacuo*. Several recrystallisations from ethanol to free the material from a trace of bright yellow impurity gave *p*-dimethylaminophenylacet-thiomorpholide (16 g.) as colourless prisms. No glyoxylthiomorpholide could be found in the filtrates from the ethanol crystallisation. *p*-Dimethylaminophenylglyoxylthiomorpholide (1·2 g.), m. p. 156°, was however recovered by working up the original reaction filtrate.

(d) *Propiophenone.* Propiophenone (13·0 ml.), sulphur (9·6 g.), and morpholine (18·0 ml.) were boiled under reflux for 7 hr. After cooling, the product was washed with water to remove morpholine, and the residual dark oil was extracted several times with ether. The ether solution was decanted from brown tar, filtered (charcoal), and evaporated to give a brown oil. After several days this deposited crystals. The semi-solid mass was lixiviated with ethanol and filtered to give an almost colourless solid (3·0 g.). Crystallisation from ethanol gave *benzoylacet-thiomorpholide* (XV) as almost colourless prisms, m. p. 129—130° (Found: C, 62·9; H, 6·1; O, 13·4; S, 13·2. $C_{13}H_{15}O_2NS$ requires C, 62·6; H, 6·1; O, 12·9; S, 12·9%).

(e) p-*Dimethylaminopropiophenone.* (i) *p*-Dimethylaminopropiophenone[10] (35·4 g.), sulphur (19·2 g.), and morpholine (36 ml.)were boiled under reflux for 13 hr., cooled somewhat, diluted with an equal volume of ethanol, and left overnight. The solid was filtered off, washed with a little ethanol, recrystallised from a small volume of ethanol, and suspended in water (400 ml.), and 2N-hydrochloric acid was added cautiously with stirring until the bright yellow finely divided material was dissolved, leaving brownish crystals undissolved. This solid was filtered off, washed with water, and after several crystallisations from ethanol (charcoal) gave p-*dimethylaminobenzoylacet-thiomorpholide* (XIV) (16 g.) as almost colourless needles, m. p. 156° (Found: C, 61·6; H, 6·9; O, 10·9; S, 10·8. $C_{15}H_{20}O_2N_2S$ requires C, 61·6; H, 6·9; O, 11·0; S, 11·0%). The aqueous filtrate was basified (ammonia) at 0°. The yellow precipitate was filtered off, washed with water, dried *in vacuo*, dissolved in glacial acetic acid (100 ml.), and diluted with water (350 ml.). After 1 hr., the bright yellow precipitate was filtered off and recrystallised from ethanol to give p-*dimethylaminocinnamthiomorpholide* (1·5 g.) as deep yellow plates, m. p. 170° (Found: C, 65·0; H, 6·9; N, 10·4; S, 11·3. $C_{15}H_{20}ON_2S$ requires C, 65·1; H, 7·3; N, 10·2; S, 11·6%). The aqueous acetic acid filtrate was further diluted with water (800 ml.), charcoal (2 g.) was added, and after ¼ hr. the solution was filtered and basified (ammonia) and the almost colourless precipitate was filtered off, washed with water, dried *in vacuo* (11·5 g.), and recrystallised from a small volume of ethanol to give β-p-*dimethylaminophenylpropionthiomorpholide* (XIII) as colourless needles, m. p. 117° (Found: C, 64·6; H, 7·9; N, 10·3; S, 11·3. $C_{15}H_{22}ON_2S$ requires C, 64·8; H, 7·9; N, 10·1; S, 11·5%).

(ii) With addition of nitrobenzene. *p*-Dimethylaminopropiophenone (35·4 g.), sulphur (19·2 g.), morpholine (36·0 ml.), and nitrobenzene (30·0 ml.) were boiled under reflux for 17 hr. While still warm the mixture was diluted with an equal volume of ethanol. After being kept overnight, the resulting solid was filtered off, washed with ethanol, and recrystallised from ethanol (*ca.* 2 l.) to give *p*-dimethylaminobenzoylacet-thiomorpholide (36 g.) as pale orange needles, m. p. 152—154°. Further crystallisation raised the m. p. to 155—156° but did not entirely remove the orange colour. The filtrate from the first ethanol crystallisation was taken down to dryness, and the residual solid (5 g.), a mixture of the benzoylacet-thiomorpholide, sulphur, and a dark red substance, was freed from the first by warming it to *ca.* 80° with excess of 2N-hydrochloric acid in which the thiomorpholide is soluble. The material insoluble in 2N-hydrochloric acid was filtered off and washed with a few ml. of carbon disulphide to free it from sulphur. The residual dark red material (0·5 g.) was recrystallised from ethanol to give a *substance* as reddish-purple needles, m. p. 208° (Found: C, 52·1; H, 4·2; O, 0; N, 5·5; S, 37·9. $C_{11}H_{11}NS_3$ requires C, 52·2; H, 4·4; N, 5·5; S, 38·0%).

(iii) In presence of excess of hydrogen sulphide. *p*-Dimethylaminopropiophenone (35·4.), sulphur (19·2 g.), and morpholine (36 ml.) were boiled under reflux for 7 hr., while a slow stream of hydrogen sulphide was passed through. Working up as described under (i) gave *p*-dimethylaminobenzoylacet-thiomorpholide (11 g.), *p*-dimethylaminocinnamthiomorpholide (3·8 g.) and β-*p*-dimethylaminophenylpropiothiomorpholide (19·6 g.).

(f) p-*Dimethylaminobutyrophenone*. *p*-Dimethylaminobutyrophenone[10] (38·2 g.), sulphur (9·6 g.), morpholine (36·0 ml.), and nitrobenzene (240 ml.) were boiled under reflux for 6 hr. The dark product was steam-distilled; the residual oil partially solidified after several days. The black semi-solid mass was lixiviated with acetone and filtered. The discoloured fawn solid (20 g.) was washed cautiously with acetone and with ethanol, and crystallised (charcoal) from ethanol to give β-p-*dimethylaminobenzoylpropionmorpholide* (XVII) (17 g.) as straw-coloured prisms, m. p. 169° (Found: C, 66·7; H, 7·7; O, 16·6; N, 9·4; S, 0. $C_{16}H_{22}O_3N_2$ requires C, 66·2; H, 7·6; O, 16·6; N, 9·7%).

Behaviour of Phenylglyoxylthiomorpholide towards Hydrogen Sulphide.—Phenylglyoxylthiomorpholide (10 g.) and morpholine (10 ml.) were boiled under reflux for 4 hr., while a slow current of hydrogen sulphide was passed through. After cooling, the yellow mixture was diluted with water. The oil which separated immediately solidified and was filtered off, washed, and dried *in vacuo*. The crude product had m. p. 103—105°. Crystallisation from ethanol gave recovered phenylglyoxylthiomorpholide (8·5 g.), m. p. and mixed m. p. 114°.

Reaction of Phenylglyoxylthiomorpholide with Sulphur and Hydrogen Sulphide.—Phenylglyoxylthiomorpholide (20 g.), sulphur (1·6 g.), and morpholine (10 ml.) were boiled under reflux for 4 hr. while a slow current of hydrogen sulphide was passed through. The product was cooled and washed with water to remove morpholine. The residual dark oil was dissolved in a little ethanol and left overnight. The brown crystals (15 g.) were filtered off and washed with ethanol. Further crystallisations from ethanol (charcoal) gave recovered phenylglyoxylthiomorpholide (4 g.; m. p. 112—113°) and pale yellow crystalline material (7·5 g.) shown by ultraviolet spectrum to contain 29·6% of phenylglyoxylthiomorpholide. From it by fractional crystallisation there was obtained colourless phenylacet-thiomorpholide (3·4 g.), m. p. and mixed m. p. 77—79°.

Behaviour of p-*Dimethylaminophenylglyoxylthiomorpholide towards Sulphur and Hydrogen*

Sulphide.—*p*-Dimethylaminophenylglyoxylthiomorpholide (10 g.), sulphur (1·5 g.), and morpholine (6·0 ml.) were boiled under reflux for 4 hr. while a slow current of hydrogen sulphide was passed through. After cooling, the mixture was diluted with an equal volume of ethanol. The solid was filtered off and separated by the acetic acid method (see above) to give recovered glyoxylthiomorpholide (6·0 g.; m. p. and mixed m. p. 157—159°) and *p*-dimethylaminophenylacet-thiomorpholide (1·2 g.; m. p. and mixed m. p. 139—140°).

Behaviour of p-*Dimethylaminobenzoylacet-thiomorpholide towards Sulphur and Hydrogen Sulphide.*—*p*-Dimethylaminobenzoylacet-thiomorpholide (15 g.), sulphur (1·6 g.), and morpholine (10 ml.) were boiled under reflux for 5 hr. while a current of hydrogen sulphide was passed. The product, recrystallised from ethanol, gave recovered benzoylacet-thiomorpholide (9·0 g.; m. p. 153—154°). The ethanol filtrates were taken down to dryness. The dark residue was washed with water and dissolved in glacial acetic acid (25 ml.), the solution was diluted with water (200 ml.) and filtered twice (charcoal) to remove tar, and the filtrate was neutralised with ammonia. The precipitated solid (0·5 g.) was filtered off, washed with water and recrystallised from ethanol to give β-*p*-dimethylaminophenylpropiothiomorpholide (0·2 g.), m. p. and mixed m. p. 115—116°.

p-*Dimethylaminophenyldithioglyoxylmorpholide* (VII) *from the Monothiomorpholide* (VI).—The monothiomorpholide (2·7 g.), phosphorus pentasulphide (3·0 g.), and dry benzene (50 ml.) were boiled under reflux for ½ hr. The deep red solution was filtered from insoluble matter and evaporated to dryness. The dark red residue was recrystallised twice from ethanol, to give *p*-dimethylaminophenyldithioglyoxylmorpholide (0·6 g.), m. p. and mixed m. p. 196—197° (Found: S, 20·65%).

Hydrolysis of p-*Dimethylaminophenylglyoxylthiomorpholide to* p-*Dimethylaminophenylglyoxylic Acid.*—*p*-Dimethylaminophenylglyoxylthiomorpholide (5·56 g.), potassium hydroxide (1·12 g.) in water (2 ml.), and ethanol (50 ml.) were boiled under reflux for 1½ hr. The ethanol was removed *in vacuo* and the residue stirred with water and filtered. The solid was dried *in vacuo* (4·3 g.). It was expected that this would be substantially *p*-dimethylaminophenylglyoxylmorpholide (VIII) but crystallisation from ethanol gave yellow material (3·1 g.), m. p. 120—130°, containing 4·8% of S. It was boiled with potassium hydroxide (2·24 g.) in water (3 ml.) and ethanol (50 ml.) for 4 hr. On cooling, colourless plates (1·4 g.) separated. These were filtered off and recrystallised from ethanol, to give ***potassium*** p-***dimethylaminophenylglyoxylate***, m. p. 300° (Found: C, 51·3; H, 4·6; N, 6·1. $C_{10}H_{10}O_3NK$ requires C, 52·0; H, 4·3; N, 6·1%). It was dissolved in a little water and just acidified by acetic acid. *p*-Dimethylaminophenylglyoxylic acid separated as golden-yellow plates, which after crystallisation from ethanol had m. p. 185—186°, not depressed on admixture with an authentic specimen prepared by Staudinger's method.[11]

p-*Dimethylaminophenylglyoxylmorpholide.*—The thiomorpholide (2·78 g.), silver acetate (3·34 g.), water (5 ml.), and ethanol (50 ml.) were boiled under reflux for 1½ hr. The precipitated silver sulphide was filtered off and the pale yellow filtrate evaporated to dryness. The residue was stirred with water, and the solid was filtered off, dried in the air (2 g.), and recrystallised from a small volume of ethanol, to give p-*dimethylaminophenylglyoxylmorpholide* (VIII) as almost colourless needles, m. p. 140° (Found: C, 63·9; H, 6·9; N, 10·7; O, 18·4. $C_{14}H_{18}O_3N_2$ requires C, 64·1; H, 6·9; N, 10·7; O, 18·3%).

Hydrolysis of Phenylglyoxylthiomorpholide.—Phenylglyoxylthiomorpholide (5·7 g.), potassium hydroxide (6·7 g.) in water (5 ml.), and ethanol (50 ml.) were boiled under reflux for 4 hr. The ethanol was removed by distillation and the residue dissolved in a little water, acidified with hydrochloric acid, and extracted thrice with ether. The ether extracts were dried (Na_2SO_4) and filtered (charcoal) and the ether was distilled off to leave an oil (3·2 g.) which rapidly solidified and after crystallisation from carbon tetrachloride gave mandelic acid (0·9 g.) as colourless plates, m. p. and mixed m. p. 115—116·5° (Found: C, 63·0; H, 5·2; N, 0. Calc. for $C_8H_8O_3$: C, 63·5; H, 5·3%).

Phenylglyoxylmorpholide.—Phenylglyoxylthiomorpholide (5·9 g.), silver nitrate (8·5 g.) in water (10 ml.), and ethanol (125 ml.) were boiled under reflux for ½ hr. The precipitated silver sulphide was filtered off and the filtrate was evaporated to dryness, diluted with water, and extracted twice with ether. The ether extracts were dried (Na_2SO_4) and evaporated to give an oil (4·3 g.) which slowly solidified and was recrystallised from a large volume of light petroleum

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[11] Staudinger, *Ber.*, 1909, **42**, 3489.

(b. p. 60—80°) to give *phenylglyoxylmorpholide* (XII) as colourless needles, m. p. 50—51° (Found: C, 66·3; H, 6·0; O, 21·3; N, 6·4. $C_{12}H_{13}O_3N$ requires C, 65·8; H, 5·9; O, 21·9; N, 6·4%).

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