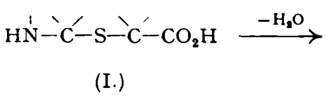
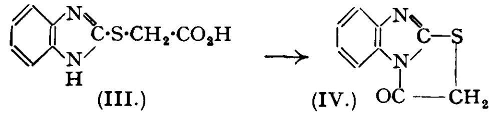
159. *Anhydro-compounds from Nitrogen-containing Derivatives of Thioglycollic Acid. Part I. Pyridine and Quinoline Compounds.*

By G. F. Duffin and J. D. Kendall.

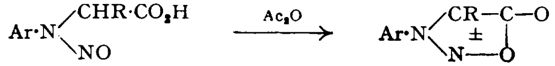
Like (2-pyridylthio)acetic acid (Koenigs and Geisler, *Ber.*, 1924, **57**, 2076), (2-quinolylthio)acetic acids unsubstituted in the 8-position react with acetic anhydride to give orange-yellow unimolecular anhydro-compounds. Similar, but less stable, compounds are obtained from α-(2-quinolylthio)-propionic and -*n*-butyric acids, but not from (4-quinolylthio)acetic acids. The properties of the anhydro-compounds are best explained on the basis of cyclic meso-ionic structures.

When a compound containing the system (I) is subjected to the action of a dehydrating agent, water is normally eliminated between the imino- and carboxyl groups, and a substituted thiazolidone (II) formed; *e.g.*, (2-benziminazolylthio)acetic acid (III), when heated with acetic anhydride, readily gives (IV) (Kendall and Duffin, B.P. 634,951).


(I.) (II.)


(III.) (IV.)

If no hydrogen atom, or group which can be eliminated easily, is attached to the nitrogen atom in (I), ring closure of this type is impossible. Earl and Mackney (*J.*, 1935, 899) have shown, however, that *N*-aryl-*N*-nitrosoglycines (V), which contain the system $O{:}N{\cdot}\dot{N}{\cdot}\dot{C}H{\cdot}CO_2H$, and cannot undergo normal ring closure without molecular rearrangement, are readily dehydrated by acetic anhydride to give unimolecular compounds now known as "sydnones." Baker, Ollis, and Poole (*J.*, 1949, 307; 1950, 1542) have proposed for these compounds a cyclic meso-ionic structure which is the hybrid of a number of contributing ionic forms and may be conveniently represented as (VI).

(V.)

(VI.)

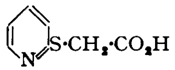
In the series of communications, of which this is Part I, the results are described of the action of dehydrating agents on various derivatives of thioglycollic acid which cannot undergo normal ring closure, *e.g.*, heterocyclic compounds of the type (VII) which contain the system $\cdot N{:}C{\cdot}S{\cdot}C{\cdot}CO_2H$, and (arylazothio)acetic acids containing the system $\cdot N{:}N{\cdot}S{\cdot}C{\cdot}CO_2H$. Although in some systems dehydration gives compounds with the characteristics of cyclic meso-ionic structures, yet the formation of these is not general, as shown in subsequent communications.

Koenigs and Geisler (*loc. cit.*) heated (2-pyridylthio)acetic acid (VIII) with acetic anhydride, and obtained a yellow compound which could be crystallised unchanged from ethanol, and which they regarded as the thiophen derivative (IX). Analysis indicated that the compound was formed by loss of a molecule of water from one molecule of the acid and it was unimolecular in phenol. With hydrochloric acid the anhydro-compound was reconverted into (VIII), and concentrated sulphuric acid gave 2-methylthiopyridine and carbon dioxide. Phenylhydrazine was reported to give a phenylhydrazone.

Tschitschibabin and Woroshtzow, jun. (*Ber.*, 1933, **66**, 364), showed that the anhydro-compound was not (IX) since it was insoluble in cold alkali, did not give a dye on oxidation, had a molecular weight in nitrobenzene double that of (IX), and even with water readily reverted to the original (2-pyridylthio)acetic acid. An unequivocal synthesis of (IX) also proved that this was different from the product obtained from (VIII), and it was shown that (3 : 5-dibromo-2-pyridylthio)acetic acid with acetic anhydride gave a dibromo-compound with similar properties to that obtained from (VIII). Tschitschibabin and Woroshtzow, therefore, regarded the yellow compound as a keten derivative (X) and attributed its stability towards ethanol to the presence of the tertiary amino-group (cf. Staudinger, *Ber.*, 1907, **40**, 1145). They ascribed their failure to obtain a similar type of anhydro-compound from (3-pyridylthio)-acetic acid to the 3-position in pyridine being unfavourable to keten formation.

When (2-quinolylthio)acetic acid is dissolved in acetic or propionic anhydride, and the solution warmed, it rapidly becomes deep yellow, and orange-yellow crystals separate. Similar compounds are also obtained from other (2-quinolylthio)acetic acids with methyl substituents in both the pyridine and the benzene ring, provided, however, that no substituent is present in the 8-position. Reaction products are also obtained from α-(2-quinolylthio)-propionic and -*n*-butyric acids, but not from (4-quinolylthio)acetic acid. No reaction occurs when either ethyl (2-quinolylthio)acetate or (2-quinolylthio)acetamide is heated with acetic anhydride. Owing to difficulties of preparation of the acid, it has not yet proved possible to study the reaction between α-(2-quinolylthio)*iso*butyric acid and acetic anhydride.


(VII.)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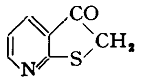
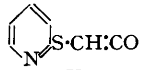

(IX.)


(X.)

(Y = Remainder of heterocyclic nucleus.)

The reaction between (2-quinolylthio)acetic acids and acetic anhydride is facilitated by a tertiary base, proceeding in the cold in the presence of pyridine, but is inhibited if a mineral acid is present. When inorganic dehydrating agents, *e.g.*, thionyl chloride or phosphoric oxide, are employed instead of acetic anhydride, no orange-yellow compounds are obtained, thionyl chloride and (2-quinolylthio)acetic acids giving, in pyridine, brown powders whose constitutions are still being investigated.

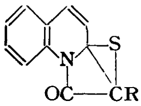
Analyses of the yellow compounds from α-(2-quinolylthio)-acids and acetic anhydride indicate that, like the product from (2-pyridylthio)acetic acid, they are anhydro-compounds formed by loss of one molecule of water from one molecule of acid. In general, they are insoluble in water and, with the exception of the products from α-(2-quinolylthio)-propionic and -butyric acids, sparingly soluble in cold organic solvents, but they can be recrystallised readily from hot ethanol or pyridine. When heated above their melting points, the anhydro-compounds darken and decompose. The anhydro-compound from (4-methyl-2-quinolylthio)acetic acid is, however, sufficiently stable for a molecular-weight determination by the Rast method, which indicates that the compound is unimolecular in camphor. Those compounds derived from (2-quinolylthio)acetic acids with a 4-methyl substituent appear to be the most stable, and those from α-(2-quinolylthio)-propionic and -*n*-butyric acids are least stable; *e.g.*, the latter are readily hydrolysed by water or dilute hydrochloric acid, whilst the former are unaffected even by hot concentrated hydrochloric acid. With 50% aqueous sulphuric acid all these anhydro-compounds are readily hydrated to the parent acids.

Because of its ease of preparation and relative stability, the anhydro-compound from (4-methyl-2-quinolylthio)acetic acid was selected for detailed study. Hydrolysis with aqueous-alcoholic sodium hydroxide gave mainly a mixture of 4-methylquinoline-2-thiol and another product, together with a trace of (4-methyl-2-quinolylthio)acetic acid. The second compound, which was soluble in hot, but insoluble in cold alkali, gave 2-hydroxy-4-methylquinoline on oxidation. Reduction of the anhydro-compound also gave 4-methylquinoline-2-thiol, and oxidation gave 2-hydroxy-4-methylquinoline. Unlike the anhydro-compound from (2-pyridylthio)acetic acid, that from (4-methyl-2-quinolylthio)acetic acid did not react with phenylhydrazine in acetic acid. In contradistinction to Koenigs and Geisler's statement, however, the compound isolated by us from the reaction between phenylhydrazine and the anhydro-compound from (2-pyridylthio)acetic acid did not appear to be a simple phenylhydrazone, its analysis indicating that it was formed from two molecules of the anhydro-compound and one molecule of phenylhydrazine with the loss of one molecule of water.

Although there is no ketonic activity, as indicated by the phenylhydrazone test, the anhydro-compounds, like quinones or *o*-diketones, *e.g.*, isatin and alloxan (Traube, *Ber.*, 1911, **44**, 3148; Schönberg, Moubasher, and Mostafa, *J.*, 1948, 176), readily react with benzylamine to give benzaldehyde, the appropriate quinoline-2-thiol being formed at the same time. A more detailed study of this reaction and its mechanism will be reported later.

From the conditions of formation of the anhydro-compounds from α-(2-quinolylthio)-acids, it is apparent that the system $\mathrm{N{:}\overset{|}{C}{\cdot}S{\cdot}\overset{|}{C}H{\cdot}CO_2H}$ is essential for reaction, and that bonding of the nitrogen atom is involved since the steric influence of a group in the 8-position, or quaternary salt formation, inhibits reaction. The properties of the anhydro-compounds also indicate that, unless a reversible molecular rearrangement occurs on hydrolysis, the skeleton of the parent acids must be present in the anhydro-compounds. The formulation of a structure for the anhydro-compounds which accords with these facts is not simple. A linear keten formula of type (X), as suggested by Tschitschibabin and Woroshtzow for the anhydro-compound from

(2-pyridylthio)acetic acid, is clearly unsatisfactory, since it is unlikely that (*a*) a keten would be formed under the reaction conditions described, (*b*) such keten formation, if possible, would be inhibited by a methyl group in the 8-position, and (*c*) (4-quinolylthio)acetic acid, in which the electronic displacement is similar to that in (2-quinolylthio)acetic acid, would fail to give a keten under those conditions in which a keten is obtained from the latter acid. The steric effect of the 8-methyl group, the inhibition of anhydro-compound formation by quaternisation of the quinoline nitrogen atom, and the failure to obtain an anhydro-compound from (4-quinolylthio)acetic acid are, however, readily explicable on the basis of a cyclic structure containing the nitrogen atom. Such a structure, if purely covalent, might be represented by (XI) containing a three- and a four-membered ring system, or by (XII) or (XIII); (XI) is unsound on stereochemical grounds (cf. Baker *et al.*, *loc. cit.*, on the structures of the sydnones), whilst (XII) and (XIII) would involve an improbable molecular rearrangement which was reversible under conditions of hydrolysis.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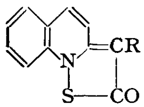
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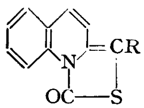
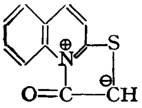

(XIII.)

Although a number of the reactions (*e.g.*, those with aqueous alkali and with benzylamine) of our anhydro-compounds are different from those of the sydnones, we consider that, like the sydnones, the anhydro-compounds are best represented by cyclic meso-ionic structures involving the hybrids of a number of resonance forms. These, like the resonance forms for the sydnones, may be formulated by (XIV)—(XX) which represent some of the dipolar contributors to the structure of the anhydro-compound from (2-quinolylthio)acetic acid. Alternatively, formula (XXI) may be used to indicate the hybrid. It will be noted that the sulphur in (XVII) bears a negative charge and has a valency shell expanded to ten electrons. A formula of this type containing a more extended conjugation might explain the colour of the anhydro-compound, and also the ease of its conversion into quinoline-2-thiol.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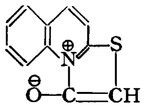
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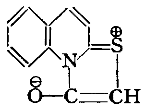
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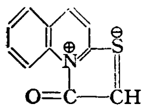
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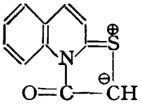
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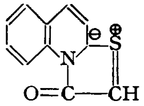
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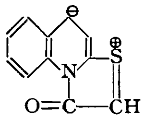
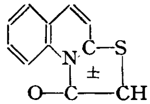

(XX.)


(XXI.)

The mechanism of formation of the anhydro-compounds by the action of acetic anhydride on α-(2-quinolylthio)acids is obscure. Baker *et al.* (*loc. cit.*) have suggested that the sydnones are formed from *N*-nitrosoglycines and acetic anhydride *via* mixed anhydrides, but it is not definite that such anhydrides are intermediates in our reaction, particularly as compounds like (4-pyridylthio)- and (4-quinolylthio)-acetic acids, which should also give mixed anhydrides, are recovered unchanged from boiling acetic anhydride.

EXPERIMENTAL.

Anhydro-compound from (2-Pyridylthio)acetic Acid.—A solution of (2-pyridylthio)acetic acid (1·5 g.) (Koenigs and Geisler, *loc. cit.*) in acetic anhydride (8 c.c.) was heated rapidly to boiling and then cooled; a mass of yellow crystals separated. Recrystallisation from ethanol gave yellow needles (1·0 g., 74%), m. p. 180°.

Action of Phenylhydrazine on Anhydro-compound from (2-Pyridylthio)acetic Acid.—When a solution of the anhydro-compound (1·0 g.) and phenylhydrazine (0·75 g.) in acetic acid (5·0 c.c.) was heated to boiling, it became red and a little hydrogen sulphide was evolved. On cooling, reddish crystals separated, which after recrystallisation gave pale red needles (0·1 g.), m. p. 163°. Dilution of the acetic acid solution precipitated more of the same *compound* (0·53 g.), m. p. 165°, in a buff-coloured form [Found : C, 61·2, 61·0; H, 4·2, 4·4; S, 16·05, 16·0. $C_{20}H_{16}ON_4S_2(= 2C_7H_5ONS + C_6H_8N_2 - H_2O)$ requires C, 61·2; H, 4·1; S, 16·3%. Koenigs and Geisler's "phenylhydrazone" requires C, 64·75; H, 4·6; S, 13·3%].

Action of Acetic Anhydride on (4-*Pyridylthio*)*acetic Acid*.—A solution of (4-pyridylthio)acetic acid (0·9 g.) (King and Ware, *J.*, 1939, 875) in dry pyridine (5 c.c.) and acetic anhydride (5·5 c.c.) was heated at 100° for 1 hour. Some decomposition appeared to take place and the solution darkened. As nothing crystallised on cooling, the solution was concentrated to half bulk by heating at 60° under reduced pressure. On cooling, crystals were deposited (0·12 g.), of m. p. 255° (decomp.) raised to 265° (decomp.) by admixture with authentic (4-pyridylthio)acetic acid. Addition of water to the mother-liquors precipitated an oily mass from which a further small quantity of the acid was obtained by extraction with boiling water.

(2-*Quinolylthio*)*acetic Acid*.—Chloroacetic acid (3·1 g.) in 10% aqueous sodium hydroxide (13·2 c.c. was added to quinoline-2-thiol (5·3 g.) in 10% aqueous sodium hydroxide (13·2 c.c.). The solution was heated at 100° for 1 hour, filtered, and cooled to 0°, and concentrated hydrochloric acid (3·5 c.c.) added. (2-*Quinolylthio*)*acetic acid* separated as an oil, which crystallised when rubbed. After filtration and drying it was obtained from benzene–light petroleum as colourless needles (5·2 g., 73%), m. p. 90° (Found : C, 60·1; H, 4·0; S, 14·6. $C_{11}H_9O_2NS$ requires C, 60·25; H, 4·15; S, 14·6%).

By an analogous process other quinoline derivatives of thioglycollic acid, described below, were prepared.

Anhydro-compound from (2-*Quinolylthio*)*acetic Acid*.—(2-Quinolylthio)acetic acid (1·0 g.) was dissolved in acetic anhydride (5 c.c.) and the solution, which rapidly became deep yellow, was brought to the boil, and then cooled quickly. Addition of ethanol (25 c.c.) precipitated a mass of yellow crystals which were filtered off and recrystallised from pyridine–ethanol, giving yellow plates of the *anhydro*-compound (0·48 g., 52%), m. p. 194° (Found : S, 16·1; N, 6·85. $C_{11}H_7ONS$ requires S, 15·95; N, 6·95%).

Anhydro-compound from (4-*Methyl*-2-*quinolylthio*)*acetic Acid*.—(*a*) (4-*Methyl*-2-*quinolylthio*)*acetic acid*, prepared from 4-methylquinoline-2-thiol, was obtained from aqueous ethanol as pale yellow needles (86%), m. p. 117° (Found : S, 13·6; N, 6·2. $C_{12}H_{11}O_2NS$ requires S, 13·75; N, 6·0%). This acid (10 g.) in acetic anhydride (50 c.c.) was heated at 100° for 5 minutes, a deep yellow colour developing and a mass of yellow crystals separating. The mixture was cooled to room temperature and filtered, and the crystals were washed with ether, and recrystallised from pyridine, giving deep yellow plates of the *anhydro*-compound (6·8 g., 74%), m. p. 227° [Found : C, 66·9; H, 4·1; S, 14·65%; *M* (Rast), 210. $C_{12}H_9ONS$ requires C, 66·95; H, 4·2; S, 14·9%; *M*, 215]. The above experiment was repeated but with propionic anhydride instead of acetic anhydride, the same product (56%) being obtained.

(*b*) (4-Methyl-2-quinolylthio)acetic acid (2·0 g.) was dissolved with stirring at room temperature in a mixture of acetic anhydride (10 c.c.) and pyridine (10 c.c.). The temperature rose to 30°, and after 15 minutes the solution, which had become deep yellow, was poured into water (50 c.c.), a yellow solid being precipitated. After filtration, and washing with water and ether, the solid was recrystallised from pyridine as yellow plates (1·24 g., 69%), m. p. 227°, identical with those obtained in the above experiments.

Action of Acetic Anhydride on (4-*Methyl*-2-*quinolylthio*)*acetic Acid in the Presence of Hydrogen Chloride*.—(4-Methyl-2-quinolylthio)acetic acid (5·0 g.) was finely powdered and added to a solution of dry hydrogen chloride (1·0 g.) in acetic anhydride (25 c.c.). After 20 minutes' heating at 100°, the resulting dark green solution was cooled to 0°; a greenish precipitate was deposited which, after filtration, washing with ethanol, and drying, had m. p. 200—204° (3·4 g.). The solid was warmed for 5 minutes with aqueous N-sodium hydroxide (34 c.c.), and the solution filtered from a small quantity of coloured material and acidified, buff-coloured needles being slowly deposited (2·9 g.), m. p. 205—210°. The structure of this unidentified acidic substance is still being investigated.

3 : 4-*Dimethylquinoline*-2-*thiol*.—Thiourea (6·8 g.) was dissolved in boiling ethanol (130 c.c.) and 2-chloro-3 : 4-dimethylquinoline (16·5 g.) (Knorr, *Annalen*, 1888, **245**, 360) added. The solution was boiled for 8 hours and poured into water (200 c.c.), the ethanol removed by distillation, 33% aqueous sodium hydroxide (20 c.c.) added, and the mixture boiled for a further hour. After cooling to room temperature, the solution was filtered, and concentrated hydrochloric acid (20 c.c.) added, 3 : 4-*dimethylquinoline*-2-*thiol* being precipitated as a yellow solid. Recrystallisation from ethanol gave yellow needles (5 g., 30%), m. p. 223° (Found : C, 69·8; H, 5·9; S, 17·4. $C_{11}H_{11}NS$ requires C, 69·8; H, 5·85; S, 16·95%).

Anhydro-compound from (3 : 4-*Dimethyl*-2-*quinolylthio*)*acetic Acid*.—This *acid*, prepared from 3 : 4-dimethylquinoline-2-thiol, was obtained from aqueous ethanol as colourless needles (62%), m. p. 134° (Found : C, 63·1; H, 5·5; S, 12·8. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). It (1·0 g.) was heated with acetic anhydride (5 c.c.) on a steam-bath for 30 minutes. The deep yellow solution was cooled and diluted with ether; a solid separated, which, after filtration and recrystallisation from pyridine, gave the *anhydro*-compound as small brown needles with a blue lustre (0·37 g., 40%), m. p. 225° (Found : C, 68·1; H, 5·0; S, 13·9. $C_{13}H_{11}ONS$ requires C, 68·1; H, 4·85; S, 14·0%).

2-*Chloro*-4 : 8-*dimethylquinoline*.—2-Hydroxy-4 : 8-dimethylquinoline (Knorr, *Ber.*, 1884, **17**, 542) (20 g.) was boiled under reflux with phosphorus oxychloride (150 c.c.) until all solid had dissolved and the evolution of hydrogen chloride had ceased. Excess of the oxychloride was removed at 80° (bath)/40 mm. Water (500 c.c.) was added to the residue, and the resulting solution made alkaline by addition of 10% aqueous sodium hydroxide. 2-*Chloro*-4 : 8-*dimethylquinoline* was precipitated as a white solid which was filtered off and recrystallised from ethanol (charcoal) as white needles (16 g., 72%), m. p. 67° (Found : Cl, 16·65. $C_{11}H_{10}NCl$ requires Cl, 16·5%).

4 : 8-*Dimethylquinoline*-2-*thiol*.—2-Chloro-4 : 8-dimethylquinoline (14 g.) was added to a boiling solution of thiourea (5·6 g.) in ethanol (100 c.c.). The solution was boiled for 2 hours and diluted with water (200 c.c.), and the ethanol removed by distillation. The aqueous solution was filtered hot; on cooling, 4 : 8-*dimethylquinoline*-2-*thiol* crystallised as yellow plates (11·7 g., 83%), m. p. 195° (Found : C, 70·3; H, 5·6; S, 16·8. $C_{11}H_{11}NS$ requires C, 69·8; H, 5·85; S, 16·95%).

Acetic Anhydride and (4 : 8-*Dimethyl-2-quinolylthio*)*acetic Acid.*—This *acid* was obtained from 4 : 8-dimethylquinoline-2-thiol as colourless needles (66%), m. p. 132° (from aqueous ethanol) (Found : C, 63·15; H, 5·25; S, 12·9. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). The acid (2 g.) was heated with acetic anhydride (10 c.c.) for 2 hours at 100°. No yellow colour developed, and on cooling and addition of ether no solid separated. The ether was removed under reduced pressure, and the solution poured into water (50 c.c.), a colourless oil, which slowly crystallised, being precipitated. After filtration, the solid was recrystallised from aqueous ethanol, giving very pale yellow needles (1·7 g., 85% recovery), m. p. 132°, identical with (4 : 8-dimethyl-2-quinolylthio)acetic acid.

Anhydro-compound from α-(2-*Quinolylthio*)*propionic Acid.*—The *acid* was prepared from quinoline-2-thiol and α-bromopropionic acid, and crystallised from aqueous ethanol as pale yellow needles (68%), m. p. 101° (Found : C, 61·6; H, 4·99. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·75%). It (1 g.) was treated in pyridine (5 c.c.) at room temperature with acetic anhydride (5 c.c.); an intense orange-yellow colour developed and a mass of orange crystals rapidly separated. These were filtered off, washed with acetone, and dried to give very small orange-red crystals of the *anhydro*-compound (0·75 g., 80%), m. p. 148° (decomp.). Recrystallisation from light petroleum–benzene gave very small pale yellow needles which became red at 122° and had m. p. 148° (decomp.) (Found : C, 67·0; H, 4·25. $C_{12}H_9ONS$ requires C, 66·95; H, 4·2%).

Anhydro-compound from α-(2-*Quinolylthio*)*butyric Acid.*—The *acid* was prepared from quinoline-2-thiol and α-bromo-*n*-butyric acid, and obtained from aqueous ethanol as pale yellow needles (60%), m. p. 114° (Found : C, 63·1; H, 5·1; S, 12·9. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). It (1·0 g.) was dissolved in pyridine (5 c.c.) at room temperature, and acetic anhydride (5 c.c.) added; an intense orange-yellow colour developed; after a few minutes a mass of orange crystals separated. These were filtered off, washed well with acetone, and dried to give very small orange-red crystals (0·65 g., 72%). Recrystallisation from light petroleum–benzene gave the *anhydro*-compound as pale yellow crystals, m. p. 161—162° (decomp.) (Found : C, 68·05; H, 4·85; S, 14·0. $C_{13}H_{11}ONS$ requires C, 68·1; H, 4·85; S, 14·0%).

Anhydro-compound from α-(4-*Methyl-2-quinolylthio*)*propionic Acid.*—The required *acid* was prepared from α-bromopropionic acid and 4-methylquinoline-2-thiol, and obtained from aqueous ethanol as very pale yellow needles (64%), m. p. 139° (Found : C, 63·4; H, 5·1; S, 13·0. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). It (4·0 g.) was treated in pyridine (12 c.c.) at room temperature with acetic anhydride (12 c.c.). A deep orange colour developed and a mass of yellow needles rapidly separated. These were filtered off, washed with ether, and dried *in vacuo* (3·6 g., 78%), m. p. 134—135°. Recrystallisation from benzene (charcoal) gave bright orange needles of the *anhydro*-compound, m. p. 135—136°. The crystals contained a molecule of acetic acid of crystallisation which was not removed by repeated crystallisation (Found : C, 62·4; H, 5·3; N, 4·6; S, 10·8. $C_{13}H_{11}ONS,C_2H_4O_2$ requires C, 62·25; H, 5·25; N, 4·8; S, 11·1%).

Anhydro-compound from α-(4-*Methyl-2-quinolylthio*)-n-*butyric Acid.*—This *acid*, prepared from 4-methylquinoline-2-thiol and α-bromo-*n*-butyric acid, was obtained as pale yellow needles from aqueous ethanol (58%), m. p. 128° (Found : C, 64·3; H, 5·8; S, 12·2. $C_{14}H_{15}O_2NS$ requires C, 64·35; H, 5·8; S, 12·25%). It (1·0 g.) was dissolved in pyridine (4 c.c.)-acetic anhydride (4 c.c.) at room temperature. A deep orange colour rapidly developed and a mass of orange needles separated. These were filtered off, washed with ether, and dried *in vacuo* (0·7 g., 74%), m. p. 133—135°. Recrystallisation from benzene–light petroleum gave orange-yellow needles of the *anhydro*-compound, m. p. 139° (Found : C, 69·1; H, 6·0; S, 13·3; N, 5·65. $C_{14}H_{13}ONS$ requires C, 69·1; H, 5·4; S, 13·2; N, 5·75%).

Acid Hydrolysis of Anhydro-compound from (4-*Methyl-2-quinolylthio*)*acetic Acid.*—Finely powdered anhydro-compound (5 g.) was added to a mixture of concentrated sulphuric acid (10 c.c.) and water (10 c.c.). The resultant yellow solution was boiled gently under reflux for 10 minutes, the yellow colour disappearing. The solution was cooled, diluted with water (100 c.c.), and filtered to remove a trace of tarry solid, and an aqueous solution of sodium acetate (50 g.) added. A solid (5·2 g., 96%), m. p. 103—107°, was precipitated, which, on recrystallisation from aqueous ethanol gave pale yellow needles, m. p. 117° alone or admixed with authentic (4-methyl-2-quinolylthio)acetic acid (Found : S, 13·7; N, 6·0. Calc. for $C_{12}H_{11}O_2NS$: S, 13·75; N, 6·05%).

Alkaline Hydrolysis of Anhydro-compound from (4-*Methyl-2-quinolylthio*)*acetic Acid.*—The anhydro-compound (10 g.) was boiled under reflux with 40% aqueous sodium hydroxide (20 c.c.), water (100 c.c.), and ethanol (100 c.c.) for 10 hours, during which it slowly dissolved to give a brown solution. Ethanol (60 c.c.) was then removed by distillation, and the solution filtered hot (charcoal). On cooling, a pale brown micro-crystalline solid separated, which on recrystallisation from benzene gave colourless needles (3·0 g.), m. p. 210°. The compound was readily soluble in hot water and hot dilute aqueous sodium hydroxide but sparingly soluble in the cold (Found : C, 73·65, 73·45; H, 5·4, 5·6; S, 5·5, 4·9; N, 8·5%). The aqueous alkaline filtrate, diluted with a solution of sodium hydrogen carbonate (20 g.), deposited a pale yellow solid; this was filtered off, washed with water, and recrystallised from ethanol as pale yellow needles of 4-methylquinoline-2-thiol (4·5 g., 60%), m. p. 264—265° alone or admixed with the authentic compound. Acidification of the aqueous filtrate with excess of hydrochloric acid gave a solid (0·05 g.) which recrystallised from aqueous alcohol as pale yellow needles, m. p. 117° alone or admixed with authentic (4-methyl-2-quinolylthio)acetic acid.

The compound (1·0 g.), m. p. 210°, obtained from the original alkaline solution, was boiled for 3 hours with concentrated nitric acid (6 c.c.) and water (40 c.c.). After filtration the solution was cooled, and colourless crystals slowly separated. Recrystallisation from water gave colourless needles (0·62 g.), m. p. 227° alone or admixed with authentic 4-hydroxy-2-methylquinoline (Found : C, 75·15; H, 5·6. Calc. for $C_{10}H_9NO$: C, 75·4; H, 5·7%).

Reduction of Anhydro-compound from (4-*Methyl-2-quinolylthio*)*acetic Acid.*—(*a*) The anhydro-compound (10 g.) was boiled with concentrated hydrochloric acid (100 c.c.) and ethanol (400 c.c.), and granulated zinc (40 g.) added. After 3 hours' heating a vigorous reaction occurred and the deep yellow colour of the solution faded. When the reaction had subsided the solution was filtered hot, and allowed to cool. Pale yellow crystals separated which, on recrystallisation from ethanol, gave pale yellow needles (4·0 g., 53%), m. p. 264—265°, alone or admixed with authentic 4-methylquinoline-2-thiol.

(*b*) A solution of the anhydro-compound (10 g.) in glacial acetic acid (100 c.c.) was warmed to 100°, and zinc dust (20 g.) added gradually; when the initial vigorous reaction had subsided the solution was filtered hot and allowed to cool, a copious pale yellow precipitate being deposited. This was filtered off, washed with acetone, and dried (7·0 g.). The solid, which had m. p. 281°, contained zinc and left a residue (20·4%) on ignition. It was dissolved in concentrated sulphuric acid (20 c.c.) at 0°, and the solution filtered from a sludge and poured on ice; a yellow solid was precipitated, which was collected and recrystallised from ethanol, giving pale yellow needles of 4-methylquinoline-2-thiol (2·95 g.), m. p. 264°.

Oxidation of Anhydro-compound from (4-*Methyl*-2-*quinolylthio*)*acetic Acid.*—(*a*) The anhydro-compound (10 g.) was boiled with concentrated nitric acid (60 c.c.) and water (400 c.c.) for 1 hour; the evolution of nitrous fumes had then ceased and the solid had dissolved completely. On cooling to 0°, a mass of white crystals slowly separated. These were filtered off and recrystallised from water as colourless needles (3·7 g., 55%), m. p. 227° alone or admixed with authentic 2-hydroxy-4-methylquinoline.

(*b*) The anhydro-compound (10 g.) was boiled with a solution of chromium trioxide (20 g.) and concentrated sulphuric acid (35 c.c.) in water (500 c.c.) for 3 hours; all the solid had then dissolved, and the solution was filtered hot and allowed to cool. A mass of crystals (4·9 g., 72%), m. p. 218—220°, was deposited which on recrystallisation from water gave colourless needles of 2-hydroxy-4-methylquinoline (2·1 g.), m. p. 227° (Found: C, 75·8; H, 5·8; N, 8·45. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·7; N, 8·8%).

Acid Hydrolysis of Anhydro-compound from α-(4-*Methyl*-2-*quinolylthio*)*butyric Acid.*—The anhydro-compound (1·0 g.) was added to concentrated hydrochloric acid (5 c.c.); a colourless solution was rapidy obtained which was evaporated to dryness, giving a pale yellow solid. The solid was dissolved in water (10 c.c.), and when kept the solution slowly precipitated pale yellow needles (0·92 g., 86%), m. p. 128° alone or admixed with authentic α-(4-methyl-2-quinolylthio)-*n*-butyric acid. Under similar conditions the anhydro-compound from α-(4-methyl-2-quinolylthio)propionic acid was also hydrolysed to the acid.

β-(2-*Quinolylthio*)*propionic Acid.*—To quinoline-2-thiol (4·83 g.) dissolved in aqueous potassium hydroxide (1·68 g. in 10 c.c. of water), β-chloropropionic acid (3·25 g.) in aqueous potassium hydroxide (1·68 g. in 10 c.c. of water) was added. The mixture was boiled for 4 hours, filtered hot, diluted with water, and acidified with concentrated hydrochloric acid (3 c.c.); a yellow oil was precipitated, which was dissolved in a mixture of benzene (50 c.c.) and ether (50 c.c.), and the solution extracted with 5% aqueous sodium hydrogen carbonate (3 × 50 c.c.). Acidification of the combined extracts gave a yellow *compound* which recrystallised from aqueous ethanol as pale yellow needles (2·3 g., 33%), m. p. 87° (Found: C, 61·7; H, 4·55; S, 14·1. $C_{12}H_{11}O_2NS$ requires C, 61·7; H, 4·75; S, 13·75%).

Failure of Acetic Anhydride to react with β-(2-*Quinolylthio*)*propionic Acid.*—A solution of this acid (1·0 g.) in acetic anhydride was heated at 100° for 1 hour. No change in colour occurred. After cooling, the solution was diluted with water, precipitating an oil which slowly crystallised in pale yellow needles (0·81 g.), m. p. 87° alone or admixed with the starting material.

Ethyl (2-*Quinolylthio*)*acetate.*—Quinoline-2-thiol (8·05 g.) was dissolved in a solution of sodium (1·15 g.) in ethanol (100 c.c.) and heated to boiling whilst ethyl chloroacetate (10·5 c.c.) was added dropwise during 10 minutes. The mixture was boiled for 3 hours, the precipitated sodium chloride removed by hot filtration, and the filtrate cooled; *ethyl* (2-*quinolylthio*)*acetate* separated as pale yellow needles (4·3 g., 35%), m. p. 91·5°, unchanged by recrystallisation from ethanol (Found: C, 62·9; H, 5·6; S, 13·1. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%).

Failure of Acetic Anhydride to react with Ethyl (2-*Quinolylthio*)*acetate.*—Ethyl (2-quinolylthio)acetate (1·0 g.) was dissolved in acetic anhydride (10 c.c.), and the solution boiled for 1 hour. No yellow colour developed and, on cooling, a mass of colourless needles was deposited, which after filtration and drying gave unchanged ethyl (2-quinolylthio)acetate (0·48 g.), m. p. 91·5°. Dilution of the filtrate with warm water gave a further quantity (0·47 g.) of the same compound.

(2-*Quinolylthio*)*acetamide.*—Quinoline-2-thiol (7·5 g.) was dissolved in a solution of sodium (1·04 g.) in ethanol (20 c.c.) and heated to boiling whilst a suspension of chloroacetamide (4·36 g.) in ethanol (20 c.c.) was added. The mixture was boiled for 3 hours and filtered hot to remove precipitated sodium chloride, and the filtrate cooled; (2-*quinolylthio*)*acetamide* separated as colourless needles (5·5 g., 58%), m. p. 126°, unchanged by recrystallisation from ethanol (Found: C, 60·1; H, 4·55; S, 14·7. $C_{11}H_{10}ON_2S$ requires C, 60·5; H, 4·6; S, 14·7%).

Non-reaction of Acetic Anhydride with (2-*Quinolylthio*)*acetamide.*—This amide (2·0 g.) was boiled under reflux with acetic anhydride (10 c.c.) for 30 minutes. There was neither development of colour nor precipitation, on cooling. The solution was diluted with ethanol and evaporated under reduced pressure, and the residual oil washed with a little ethanol, whereupon it crystallised. The crystals were filtered off and dried (1·9 g.), m. p. 100—107°; recrystallisation from benzene–light petroleum gave colourless needles, m. p. 126° (1·4 g., 70% recovery), identical with the starting material.

The authors thank the Directors of Ilford Limited for permission to publish this paper, Messrs. L. R. Brooker and T. F. W. Lawrence for the preparation of some of the intermediates employed, and Miss J. Connor and Miss W. Rhodes for the semimicro-analyses.

RODENSIDE ORGANIC LABORATORY, ILFORD LIMITED, ILFORD. [*Received, November 9th,* 1950.]