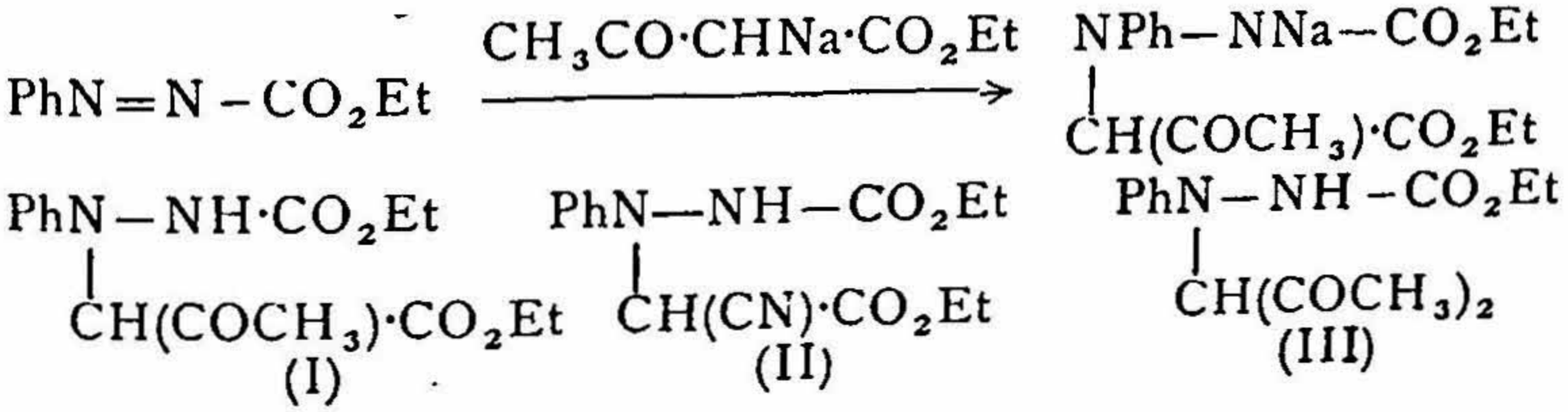
EXTENSION OF MICHAEL'S REACTION PART III

By Tejendra Nath Ghosh and Praphulla Chandra Guha.

Schlenk, Appenrodt, Michael and Thal (*Ber.*, 1914, **47**, 473) have studied the action of compounds containing the unsaturated systems C=N, N=N with sodium in ethereal solution, and the structure of the additive compounds established from a study of the products obtained by the action of water and carbon dioxide. There is no record of work in which unsaturated compounds of the above type have been made to react with the sodium derivatives of organic compounds containing active methylene groups.

In parts I and II of this series (*J. Indian Chem. Soc.*, 1930, **7**, 264-273), the action of sodium derivatives of urethane on unsaturated esters, isocyanates and isothiocyanates has been studied. The work has now been further extended to determine whether unsaturated systems like N=N, C=N, would lend themselves to ordinary Michael's condensation in forming additive compounds with sodium derivatives of acetoacetic ester, cyanacetic ester, acetylacetone and urethane.

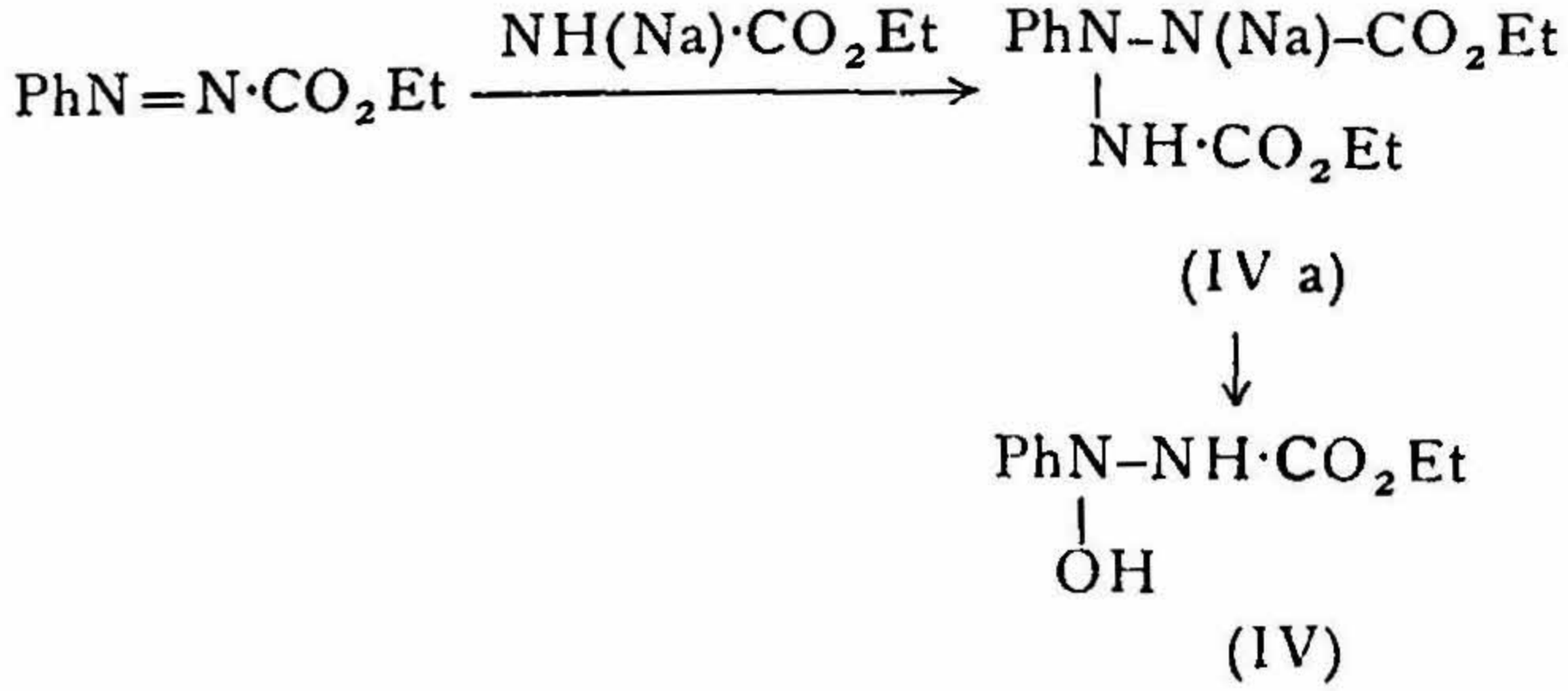
Phenyl azo-carboxylic ester reacts with the sodium derivatives of ethyl acetoacetate, ethyl cyanacetate and acetylacetone to yield β-N-carbethoxyacetylmethyl-β-phenylcarbazinic ester (I), β-N-carbethoxy-cyanomethyl- β-phenylcarbazinic ester (II) and β-N-diacetylmethyl-N-phenylcarbazinic ester (III) respectively.



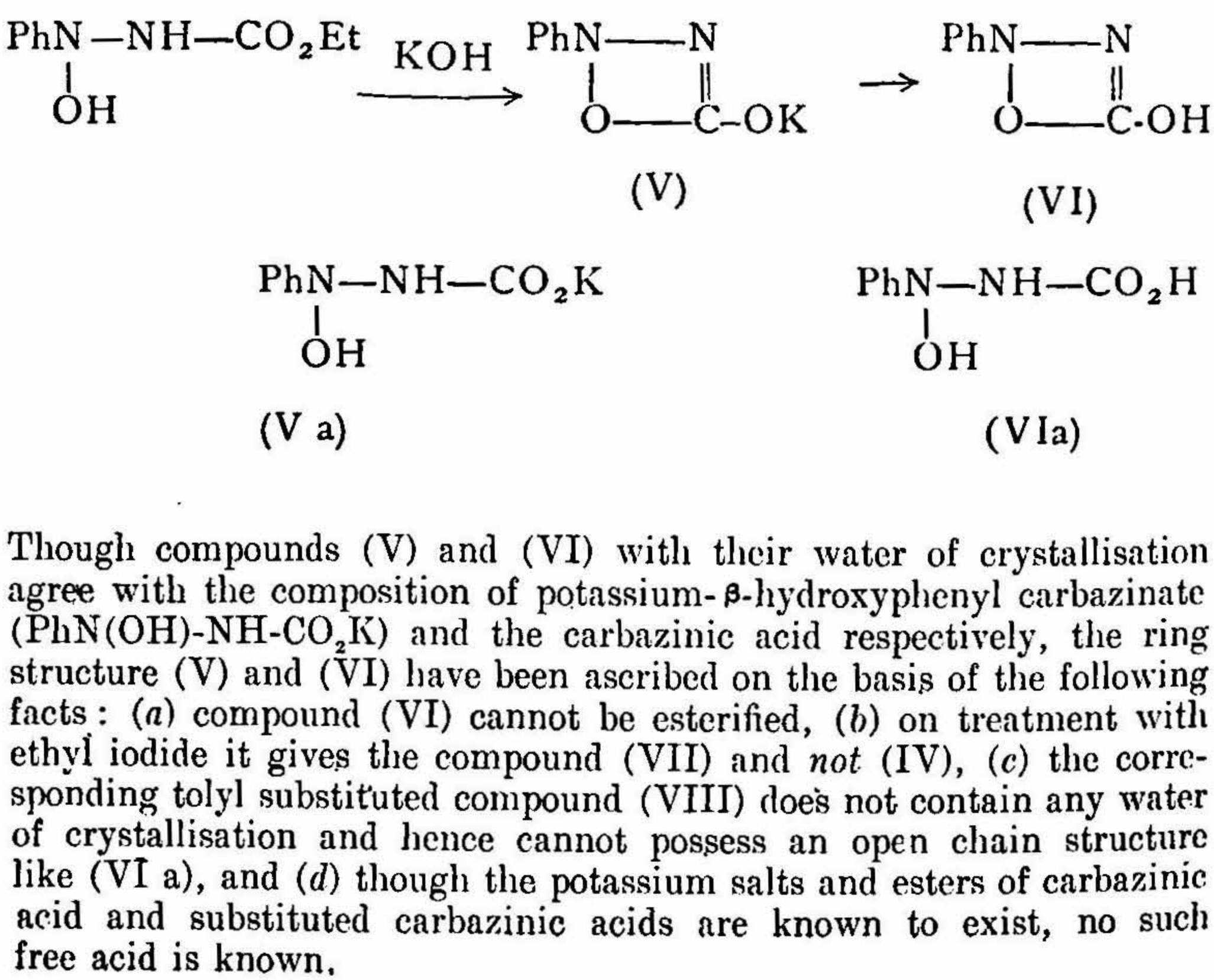
The yields of these compounds are generally very poor. They are unstable in presence of cold dilute alkali and hot acid. Decomposition of compound (I) into phenyl isocyanide on hydrolysis further confirms the direct attachment of the acetoacetic ester grouping with the β-nitrogen atom.

Ethyl phenylazocarboxylate reacts with the sodium derivative of urethane to form an unstable intermediate product (IVa) which, in

presence of acids, gets readily hydrolysed into urethane and β-N-hydroxy-β-phenylcarbazinic ester (IV).

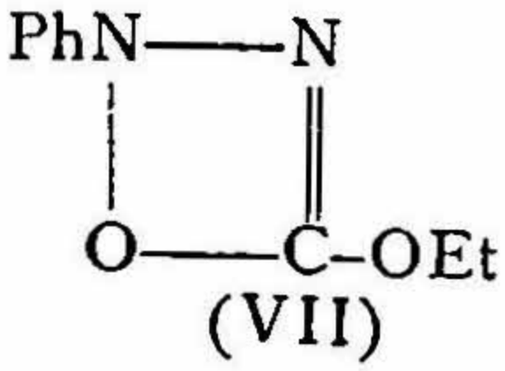


On treatment with aqueous alkali compound IV yields the sparingly soluble potassium salt (V) from which acids liberate the compound VI.

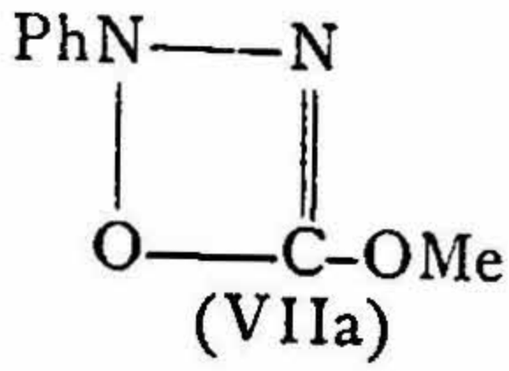


Though compounds (V) and (VI) with their water of crystallisation agree with the composition of potassium-β-hydroxyphenyl carbazinate ($PhN(OH)\text{-}NH\text{-}CO_2K$) and the carbazinic acid respectively, the ring structure (V) and (VI) have been ascribed on the basis of the following facts: (*a*) compound (VI) cannot be esterified, (*b*) on treatment with ethyl iodide it gives the compound (VII) and *not* (IV), (*c*) the corresponding tolyl substituted compound (VIII) does not contain any water of crystallisation and hence cannot possess an open chain structure like (VI a), and (*d*) though the potassium salts and esters of carbazinic acid and substituted carbazinic acids are known to exist, no such free acid is known.

The compound (V) gives with ethyl iodide and methyl iodide the corresponding ethyl and methyl derivatives (VII) and (VIIa) respectively :—

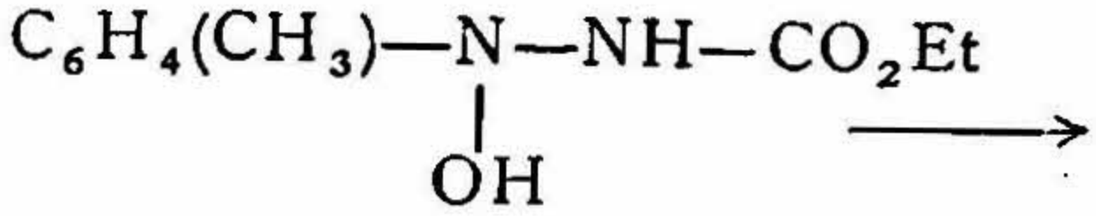


(VII)

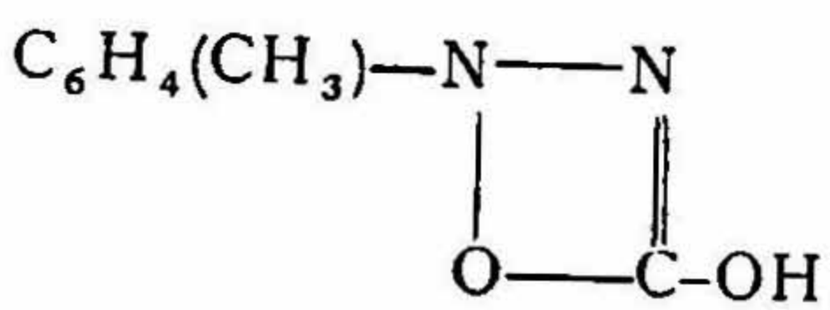


(VIIa)

Ethyl *p*-tolylazocarboxylate reacts similarly with the sodium derivative of urethane to yield the compound (VIII), the intermediate product (VIII a) could not, however, be isolated.

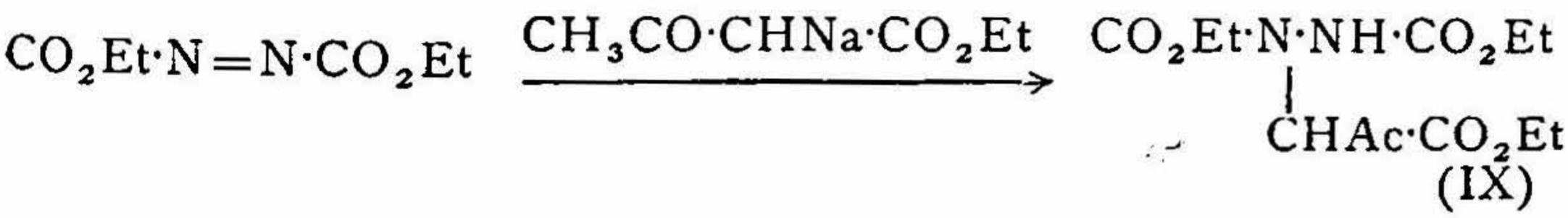


(VIIIa)



(VIII)

Ethyl azodicarboxylate $CO_2Et\text{-}N=N\text{-}CO_2Et$ with the sodium derivative of acetoacetic ester gives similarly N-carbethoxyacetylmethylhydrazodicarboxylic ester (IX).



(IX)

The conclusion to be drawn from the inactivity of azobenzene in such reactions is that for Michael's condensation with systems like (-N=N-), it is essential that there should be at least one strongly negative group attached to one of the nirtogen atoms. An analogous observation was made by Ingold and Weaver (*J. C. S.*, 1925, **127**, 378) about the inactivity of the ketens in their addition to azobenzene though the addition took place quite readily with phenylazocarboxylic ester and azodicarboxylic ester. Ingold's explanation of this difference which is based on the assumption that the carbethoxy group has much smaller affinity demand than phenyl, is equally applicable to the present instance.

It was next contemplated to study Michael's condensation with compounds containing the unsaturated grouping (-N=C-) and differently substituted by the negative groups phenyl and carboxyl e.g. compounds like (i) PhN=CHPh, (ii) $PhN=CH\cdot CO_2Et$, (iii) $CO_2Et\cdot N=CHPh$,

(iv) $PhN{=}C(CO_2Et)_2$, (v) $CO_2Et{\cdot}N{=}CH{\cdot}CO_2Et$, (vi) $CO_2Et{\cdot}N{=}C(CO_2Et)_2$. Of these above six types,[1] only compounds i and ii are known. They do not lend themselves to ordinary Michael's condensation. The inactivity of phenylazomethinecarboxylic ester as distinct from the reactivity of phenylazocarboxylic ester is perhaps due to the group ($-N{=}CH-$) inducing some basic character to the former.

As it was not possible to study Michael's condensation with compounds of type (iv), no such compound being known in literature, the addition reaction of mesoxalic ester phenylhydrazone, in which, like (iv), there are two negative (CO_2Et) groups attached to the unsaturated carbon atom, has been studied. This reacts with the sodium derivative of ethyl- acetoacetate, malonate and cyanacetate yielding additive compounds all of which get easily hydrolysed and suffer disruption giving the compound (X).

$$PhNH{\cdot}N{:}C(CO_2Et)_2 \xrightarrow{CH(Na)R{\cdot}CO_2Et} PhNH{\cdot}N(CHR{\cdot}CO_2Et){\cdot}CNa(CO_2Et)_2$$

$$\xrightarrow{\text{acid}} \underset{(X)}{PhNH-NH-CH(CO_2Et)CO_2H} \quad (R = CO_2Et,\ CN \text{ or } COCH_3).$$

$$\underset{(XI)}{PhN{=}N-CH(CO_2Et){\cdot}CO_2H} \qquad \underset{(XII)}{PhNH-NH-CH_2-CO_2H}$$

The structure of (X) is confirmed by the following facts: (1) against alkali it titrates as a monobasic acid, (2) it is oxidised by ferric chloride to an azo-derivative (XI), (3) it gets easily hydrolysed by alcoholic potash to phenylhydrazine acetic acid (XII).

It was planned at this stage to utilise the applicability of Michael's reaction with mustard oils and isocyanates (cf. Ghosh and Guha, *J. Indian Chem. Soc.*, 1930, **7**, 165) for the synthesis of pyridine derivatives. Carbethoxythiocarbimide was accordingly condensed with the

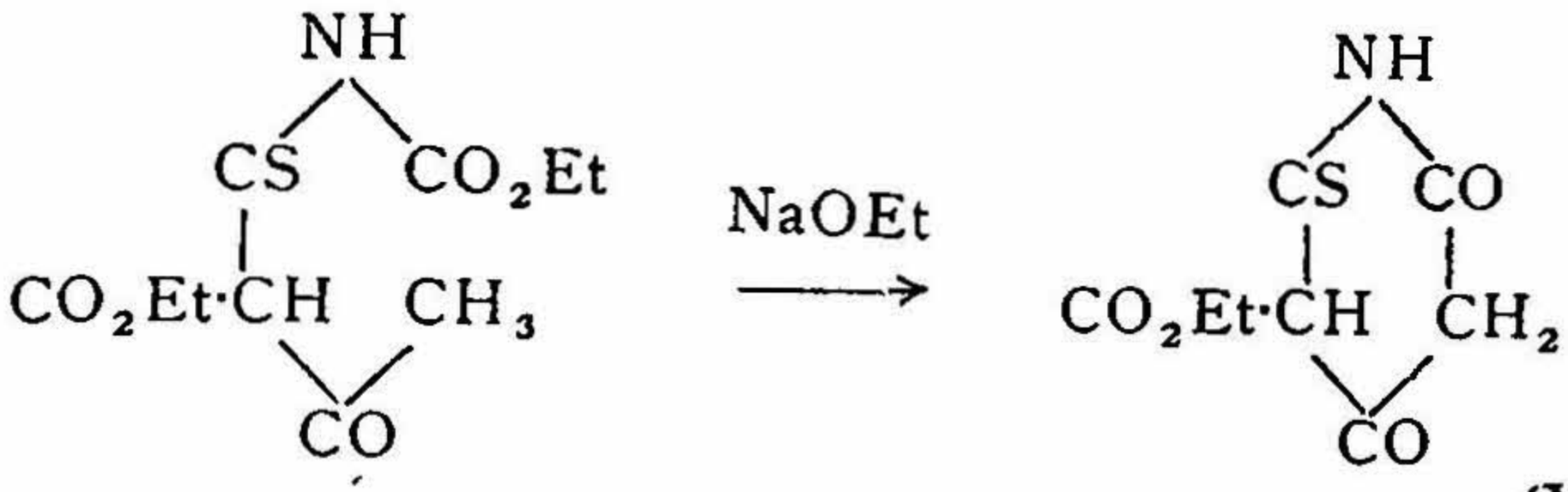
$$CO_2Et{\cdot}N{:}C{:}S \xrightarrow{CH_3CO{\cdot}CHNa{\cdot}CO_2Et} SC\begin{cases} N(Na){\cdot}CO_2Et \\ CHAc{\cdot}CO_2Et \end{cases}$$

$$\xrightarrow{\text{acid}} \underset{(XIII)}{SC\begin{cases} NH{\cdot}CO_2H \\ CHAC{\cdot}CO_2Et \end{cases}}$$

[1] Attempts are being made to prepare compounds of the type (III) to (VI) in this laboratory.

sodium derivative of acetoacetic ester resulting in the formation of thiocarbethoxy-aceto-acetyl carbamic acid (XIII).

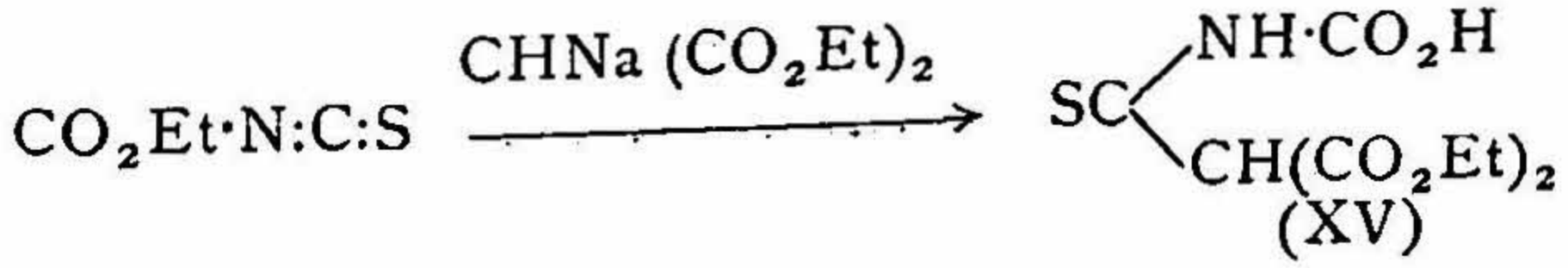
The acid (XIII) after esterification was treated with molecular proportion of sodium ethylate with the hope of getting the pyridine compound (XIV) by elimination of a molecule of alcohol (cf. Scheiber and Miessel, *Ber.*, 1915, **48**, 238; Mayuranathan and Guha, *J. Indian Inst. Sci.*, 1933, **15A**, 131);



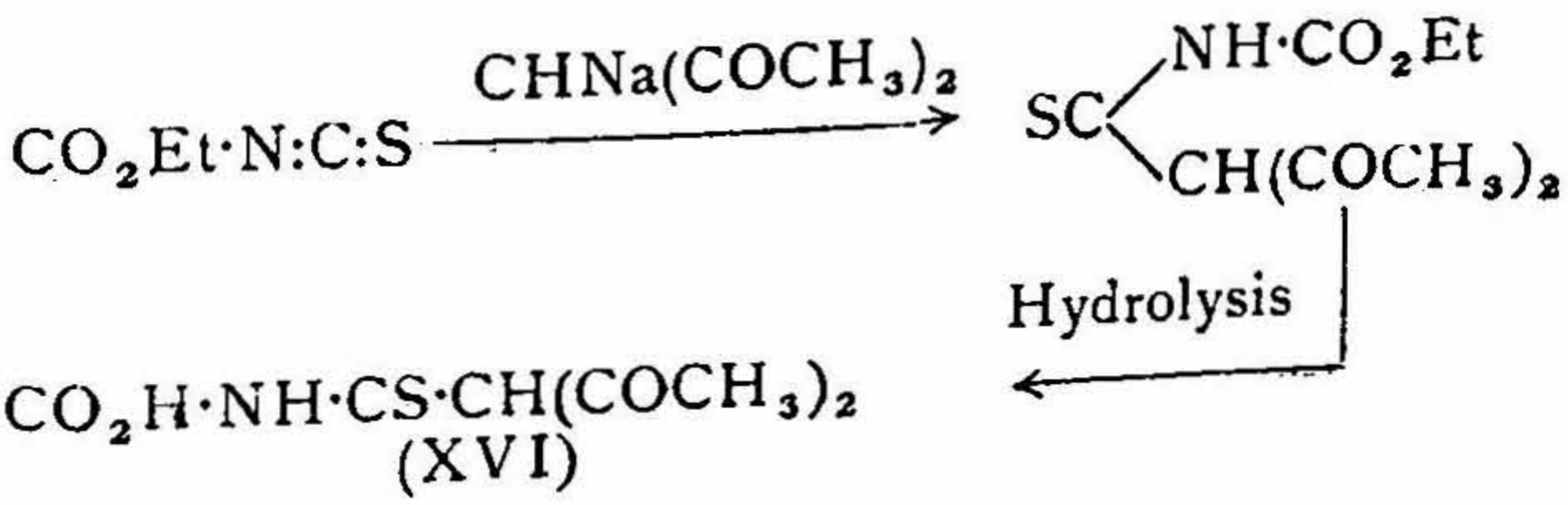
(XIV)

but, our expectation has not been fulfilled, as from the reaction mixture, only the original ester and a very small quantity of red viscous liquid could be isolated.

Compound (XIII) as also those obtained from acetylacetone and ethyl malonate, contain a free carboxyl group. It is not easy to locate definitely the position of this group in these compounds; still, by analogy with compound (XVI) in which the COOH group must have been derived from the CO_2Et attached to nitrogen—the conversion of one of the acetyl groups into a free carboxyl being unlikely—the free carboxyl groups in compounds (XIII) and (XV) have been shown attached to the end nitrogen atoms.

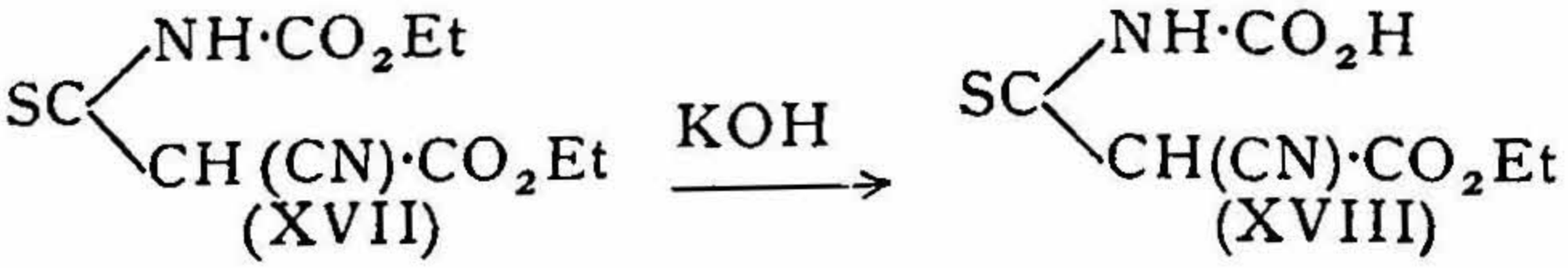


(XV)



(XVI)

Carbethoxythiocarbimide gives with ethyl cyanacetate, thiocarbethoxycyanoacetylcarbamic ester (XVII) which in presence of cold alkali gets hydrolysed into XVIII.



(XVII) (XVIII)

Compounds (XIII), (XV), (XVI) and (XVIII) could not be converted into the thioamides by the removal of carbon dioxide as they all suffered decomposition during heating.

EXPERIMENTAL.

Ethyl phenylazocarboxylate and acetoacetic ester: Formation of β-N-carbethoxyacetylmethyl-phenylcarbazinic ester (I).—Sodium wire (1.2 g.) was added to a solution of acetoacetic ester (6.5 g.) in dry ether (150 c.c.) when the sodium derivative of ethylacetoacetate separated out gradually as a white precipitate with profuse evolution of hydrogen during 2-3 hours. To this was then added ethyl phenylazocarboxylate (9 g., prepared according to the method of Widman, *Ber.*, 1895, **28**, 1927) and the reaction mixture allowed to stand overnight. The solution gradually assumed a dark violet colour, and smelt distinctly of phenylisocyanide. Next morning the precipitate was filtered, washed with ether and absolute alcohol, and then dissolved in water. The aqueous solution, on being acidified with dilute hydrochloric acid, gave a red semi-solid which after being freed from tarry matters by treatment wth ether was crystallised twice from absolute alcohol in colourless prisms m.p. 103-104°; yield 1.5 g. (Found: N, 9.204. $C_{15}H_{20}O_5N_2$ requires N, 9.09 per cent.).

N-β-carbethoxycyanomethyl-phenylcarbazinic ester (II).—Ethyl phenylazocarboxylate (9 g.) was added to dry ether (150 c.c.) containing the sodium derivative of ethylcyanacetate (6.8 g.) in suspension. After standing for 2-3 days the separated precipitate was dissolved in cold water and the aqueous solution, on acidification, gave a semi-solid which after ether treatment was crystallised from water in colourless needles m.p. 69-70° (Found : N, 14.81. $C_{14}H_{17}O_4N_3$ requires N, 14.43 per cent.).

β-N-diacetylmethyl-phenylcarbazinic ester (III).—The ester (9.0 g.) was added to an ether suspension of sodium derivative of acetylace-

tone (6.1 g.). The reaction proceeded very slowly and was complete after 48 hours. The aqueous solution of the separated sodium derivative gave on acidification a semi-solid which crystallised from alcohol in colourless needles m.p. 130-131° (Found: N, 10.34. $C_{11}H_{18}O_4N_2$ requires N, 10.07 per cent.).

β-N-hydroxy-phenylcarbazinic ester (IV).—An aqueous solution of the reddish brown sodium salt obtained similarly to the foregoing compounds from phenylazocarboxylic ester and sodium urethane, gave on acidification with dilute hydrochloric acid a dark red heavy liquid, the ethereal solution of which, on slow evaporation, deposited a reddish brown crystalline compound and was purified by crystallisation from alcohol (after animal charcoal treatment) in colourless prisms m.p. 178-179° (decomp.). It is insoluble in cold alkali and is unaffected by oxidising agents (Found: N, 14.29; C, 55.1; H, 6.30. $C_9H_{12}O_3N_2$ requires N, 14.28; C, 55.10; H, 6.12 per cent.).

Potassium-β-N-hydroxy-phenylcarbazinate (V).—The clear solution obtained by heating compound (IV) with a small quantity of normal solution of caustic potash, deposited shining colourless plates on cooling, purified further by dissolving in absolute alcohol and precipitating by ether; m.p. 135-136° (Found: N, 13.57. $C_7H_7O_3N_2K$ requires N, 13.59 per cent.). The preparation of compounds (IV) and (V) was repeated about half a dozen times.

The *compound* (VI) was obtained from an aqueous solution of the potassium salt on acidification with dilute hydrochloric acid and was crystallised from dilute alcohol in colourless needles; m.p. 214-216°. It cannot be esterified and is not oxidised by ferric chloride (Found: N, 16.70. $C_7H_6O_2N_2$, H_2O requires N, 16.66 per cent.).

Action of methyliodide on compound (V): *Formation of compound* (VIIa).—An alcoholic solution of the potassium salt (V) was boiled under reflux with an excess of methyliodide during half-an-hour. The alcoholic solution after being freed from the separated potassium iodide was evaporated to dryness; the residue crystallised from dilute alcohol in colourless needles, m.p. 128-129°. It is insoluble in alkali (Found: N, 17.15. $C_8H_8O_2N_2$ requires N, 17.07 per cent.).

The corresponding *ethyl* derivative (VII) was similarly obtained and crystallised from dilute alcohol in colourless needles, m.p. 130-131° (Found: N, 15.48. $C_9H_{10}O_2N_2$ requires N, 15.72 per cent.).

p-*Tolylazocarboxylic ester and urethane*: *Formation of compound* (VIII).—The method of procedure was the same as in the case of the previous compound (IV). The aqueous solution of the reddish brown

sodium salt gave on acidification a tarry mass which on ether treatment yielded a small quantity of brown solid crystallising from alcohol in colourless plates; m.p. 168-170°. It is soluble in cold dilute alkali and is precipitated unchanged by acids (Found : N, 17.32. $C_8H_8O_2N_2$ requires N, 17.07 per cent.).

β-N-carbethoxyacetylmethylhydrazine dicarboxylic ester (IX).—Azodicarboxylic ester (5.8 g.; prepared according to the method of Ingold *J. C. S.*, 1925, **127**, 381) was added to the sodium derivative of acetoacetic ester (5.1 g.) in ethereal suspension and the mixture allowed to stand for a day. An aqueous solution of the separated sodium derivative on acidification with dilute hydrochloric acid, gave a semi-solid which crystallised from benzene; m.p. 74-75°; yield 5 g. (Found : N, 9.03. $C_{12}H_{20}O_7N_2$ requires N, 9.21 per cent.).

Mesoxalic esterphenylhydrazone and acetoacetic ester : Formation of phenylhydrazine malonic mono ester (X).—The aqueous solution of the reaction product, on acidification, gave a precipitate which crystallised from alcohol in beautiful yellowish needles, m.p. 110-111°. It is soluble in sodium bicarbonate solution and is precipitated unchanged by acids (Found : N, 11.93; M.W. by titration, 235. $C_{11}H_{14}O_4N_2$ requires N, 11.76 per cent.; M.W., 238).

The compound (m.p. 110-111°) obtained from mesoxalic esterphenylhydrazone and the sodium derivative of malonic ester or cynacetic ester, was proved to be identical with compound (X) by the mixed melting point method and also by analysis.

The *azo-compound* (XI).—Compound (X) on being boiled with aqueous ferric chloride during two hours gave a red precipitate which crystallised from alcohol in reddish-brown prisms, m.p. 174-176° (Found : N, 11.62. $C_{11}H_{12}O_4N_2$ requires N, 11.86 per cent.).

Hydrolysis of compound (X) : *Formation of compound* (XII).—The compound (X) was heated under reflux with 15 per cent. alcoholic potash for about half-an-hour when the yellowish potassium salt separated out. It was dissolved in water and acidified with dilute hydrochloric acid when a yellow solid was obtained crystallising from alcohol in yellow needles; m.p. 152-153°. It is soluble in aqueous sodium bicarbonate (Found : N, 16.51. $C_8H_{10}O_2N_2$ requires N, 16.86 per cent.). Its identity with phenylhydrazinoacetic acid (m.p. 153°) (*Monatsh.*, **17**, 631) was established.

The *phenylhydrazine* salt was obtained by adding phenylhydrazine (1 mol.) to an ether solution of the above compound (X, 1 mol.). The white precipitate crystallised from ether in colourless plates, m.p.

124-125° (Found: N, 16.52. $C_{17}H_{22}O_4N_4$ requires N, 16.18 per cent.).

Carbethoxythiocarbimide and acetoacetic ester: Formation of thiocarbethoxyacetoacetylcarbamic acid (XIII).—The aqueous solution of the sodium derivative prepared in the usual manner, gave on acidification, a reddish yellow heavy liquid. For purification, a solution of the oil in sodium bicarbonate after being thoroughly shaken with ether was acidified with hydrochloric acid when a yellowish oil separated (Found: S, 13.44; M.W., 230. $C_8H_{11}O_5NS$ requires S, 13.73 per cent.; M.W., 233). The liquid decomposes on slow heating even under reduced pressure.

The *ethyl ester* was obtained by boiling an absolute alcoholic solution of the above acid with a small quantity of concentrated sulphuric acid during eight hours. The solution was then neutralised with calcium carbonate, and the precipitate filtered off. The clear solution after removal of alcohol was poured into water; the separated oil was washed with water and then ether extracted. The ethereal solution yielded a light brown mobile liquid which could not be distilled without decomposition (Found: S, 11.82. $C_{10}H_{15}O_5NS$ requires S, 12.26 per cent.).

Attempt to effect ring closure of the above ester.—An alcoholic solution of the ester (1 mol.) was heated under reflux for about 12 hours with sodium ethoxide (1 mol.), the alcohol distilled under reduced pressure and the solid residue dissolved in water. The aqueous solution, on acidification, yielded a reddish liquid, the alkali-insoluble portion of which was identified to be the original ester. The alkaline solution, on acidification, gave a very small quantity of reddish viscous liquid insoluble in sodium bicarbonate. It did not solidify in a vacuum desiccator on long standing. It contained nitrogen and sulphur.

Thiodicarbethoxyacetylcarbamic acid (XV).—A toluene solution of carbethoxythiocarbimide (7 g.; prepared according to the method of Doran, *J. C. S.*, 1896, **69**, 326) was added to an ether suspension of sodiomalonic ester obtained from malonic ester (8 g.) and sodium (1.15 g.) and the mixture allowed to stand overnight. Most of the separated white precipitate dissolved readily in water leaving a small portion undissolved. The aqueous solution, on acidification gave a precipitate which crystallised from alcohol in yellowish prisms m.p. 70-72°; yield 6 g. It is soluble in sodium bicarbonate solution and is precipitated unchanged by acids (Found: S, 11.92; M.W. by titration, 261. $C_9H_{13}O_6NS$ requires S, 12.16 per cent.; M.W., 263).

The water insoluble portion crystallised from acetic acid in beautiful colourless plates; m.p. 164-165°. It contains sulphur but no

nitrogen. The compound could not be further studied due to its extremely poor yield.

Thiodiacetylacetocarbamic acid (XVI).—The aqueous solution of the sodium derivative on acidification, gave a yellow precipitate which crystallised from dilute alcohol in yellow needles, m.p. 121-122° (decomp.) Found : S, 15.45; M.W. by titration, 201. $C_7H_9O_4NS$ requires S, 15.76 per cent.; M.W., 203).

Thiocarbethoxycyanoacetylcarbamic ester (XVII).—The aqueous solution of the sodium derivative gave on acidification, a semi-solid which on keeping turned into a crystalline product. It crystallised from acetic acid in colourless prisms m.p. 152-153° (decomp.) (Found : N, 11.14. $C_9H_{12}O_4NS$ requires N, 11.47 per cent.). It is insoluble in alkali.

Hydrolysis of (XVII) *into thiocarbethoxycyanoacetylcarbamic acid* (XVIII).—A mixture of the above ester (3 g.) and N/10 caustic potash solution (50 c.c.) was allowed to stand for two days and then acidified with dilute hdyrochloric acid; the resulting precipitate crystallised from alcohol in colourless prisms m.p. 158-160° (decomp.) (Found : N, 12.62; M.W. by titration, 214. $C_7H_8O_4N_2S$ requires N, 12.96 per cent.; M.W., 216).

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