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# Reactions of Arylaminomethylenemalonates with Amines*†

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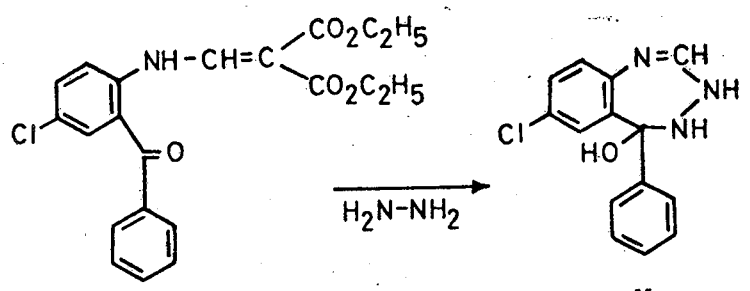
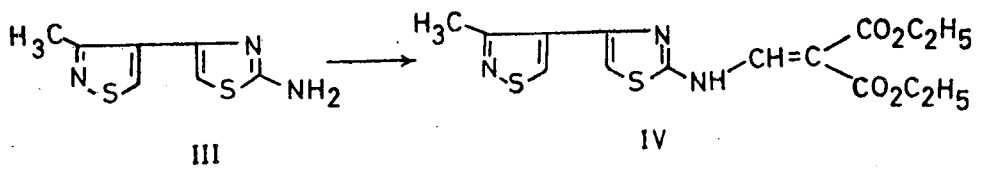
**The reaction of arylaminomethylenemalonates with amines can in some cases lead to amidines, e.g. reaction of diethyl N-[4-(3-methyl-4-isothiazolyl)-2-thiazolyl]aminomethylenemalonate (IV) with morpholine and pyrrolidine gives the corresponding amidines besides 2-amino-4-(3-methyl-4-isothiazolyl) thiazole (III), the starting substrate for the preparation of (IV). The reaction of IV with N-methylpiperazine gives only III. Mechanism to explain the regeneration of III in the reaction of IV with amines has been suggested.**

IN a recent publication, Podesva *et al.*[1] have reported that the reaction of 5-chloro-2-(2',2'-biscarboethoxyvinylamino) benzophenone (I) with hydrazine hydrate leads to the triazepine (II), by initial displacement of diethylmalonate followed by cyclization. We have carried out extensive studies on the reaction of arylaminomethylenemalonates with secondary bases and have realized, besides this novel formation of amidines, two other reaction pathways.

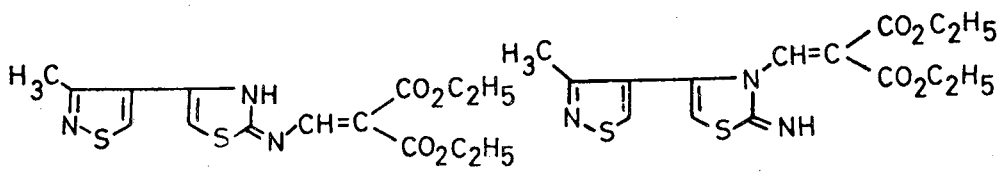
The substrate for our studies was 2-amino-4-(3-methyl-4-isothiazolyl) thiazole (III). This was prepared from the previously described[2] 4-acetyl-3-methylisothiazole by a standard two-step sequence of bromination followed by condensation with thiourea. Reaction of this with diethyl ethoxymethylenemalonate gave the aminomethylenemalonate (IV). The NMR spectrum of this compound helped to assign structure (IV) to the product uniquely, eliminating the tautomeric structure (V) and the isomeric structure (VI). Thus the olefinic signal was seen at 8·78 ppm as a doublet ($J$ = 13 *cps*) and the NH as a broad doublet at 11·47 ppm ($J$ = 13 *cps*). Addition of $D_2O$ caused the disappearance of the latter and the collapse of the former to a singlet.




I II

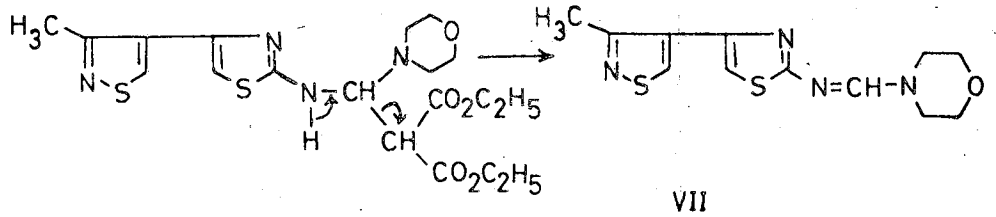



III IV

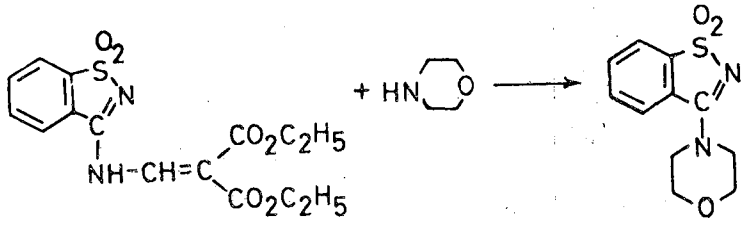



V VI

*Contribution No. 166 from CIBA Research Centre.
†Part II in Isothiazole Series; for Part I see ref. 2.



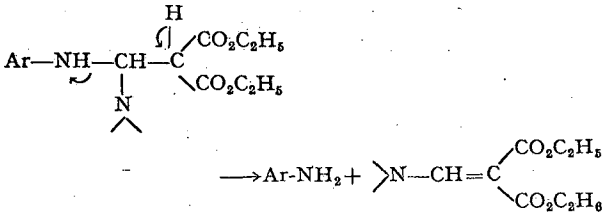
VII



VIII IX

It was realized at the outset that there are several possible modes of attack by an amine on such a system (IV) — from simple amide formation to more complex changes. In the event, reaction of (IV) with morpholine gave a mixture of products which showed two spots on alumina TLC. The slower moving one corresponded to compound (III). The faster moving component, which formed the major product, was easily obtained by chromatography on an alumina column. It analysed for the formula $C_{12}H_{14}N_4OS_2$, and in the NMR spectrum, showed a singlet (1H) at 8·33 ppm. This led to the amidine structure (VII) for the compound. Compound (IV) behaved similarly towards pyrrolidine. Mechanistically, the amidine (VII) would arise from an initial Michael addition to intermediate (A) followed by elimination of malonate.

The following alternate mode of collapse of the intermediate is also possible, which would explain the regeneration of (III) in the reaction of (IV) with amine*:



In the case of N-methylpiperazine, the only isolable product was (III), arising by the second mode of fragmentation.

The course of the reaction was entirely different, however, when the nucleus was activated for a direct nucleophilic attack. Treatment of the saccharin derivative (VIII) with morpholine gave (IX) as the only isolable compound. The identity was established by comparison with a sample synthesized from pseudosaccharin chloride and morpholine. Evidently, this arises by addition of morpholine to C=N, followed by elimination of diethyl aminomethylenemalonate.

We have attempted to extend the formamidine synthesis to other aminoheterocycles. We obtained very satisfactory yields in the case of 2-amino-1,3,4-oxadiazole and 2-aminobenzothiazole derivatives (unpublished observations of K. Nagarajan, M. D. Nair & V. Ranga Rao). The diethyl methylenemalonate derivatives of aniline, 2-aminopyridine, 3-aminopyridine and 2-aminopyrimidine did not afford the desired formamidine derivatives. A poor yield of the expected product was obtained when diethyl (4-pyridylamino)-methylenemalonate was allowed to react with N-phenylpiperazine.

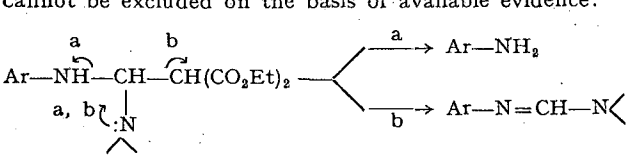
## Experimental Procedure

The NMR spectra were determined in $CDCl_3$ solution with a Varian A-60 instrument, using TMS as an internal standard. M.p.'s are uncorrected.

4-(α-*Bromoacetyl*)-3-*methylisothiazole*—4-Acetyl-3-methylisothiazole (4·2 g) in dry chloroform (20 ml) was treated gradually with bromine (4·8 g) in chloroform (25 ml) with shaking and occasional warming. The solution was finally cooled in ice, the solid filtered and washed with chloroform to yield the hydrobromide (6·6 g). The free base was liberated with aq. $NaHCO_3$ solution and recrystallized from aq. ethanol; m.p. 100-102° (Found: C, 33·14; H, 3·00; N, 6·23. $C_6H_6BrNOS$ requires C, 32·75; H, 2·75; N, 6·37%).

2-*Amino*-4-(3-*methyl*-4-*isothiazolyl*) *thiazole* (III) — A mixture of the above bromo compound (5·5 g) and thiourea (1·9 g) in ethanol (25 ml) was refluxed for 3 hr, concentrated to half the volume, and cooled. The hydrobromide crystallized on addition of ether and was recrystallized from ethanol-ether; m.p. 218-19° (decomp.), darkening above 190° (Found: C, 30·43; H, 3·14; N, 14·85. $C_7H_7N_3S_2.HBr$ requires C, 30·23; H, 2·90; N, 15·11%).

*The referee has suggested that the possibility of III and VII arising from the common intermediate as follows cannot be excluded on the basis of available evidence:



We feel, however, that because of the basic conditions employed, the reaction is more likely to be initiated by the abstraction of an acidic proton.

The hydrobromide was treated with $NaHCO_3$, and the base filtered and recrystallized from ethyl acetatehexane; yield 3·5 g; m.p. 171-3°.

*Diethyl N-[4-(3-methyl-4-isothiazolyl)-2-thiazolyl]-aminomethylenemalonate* (IV) — A mixture of the above amino compound (3·2 g) and diethyl ethoxymethylenemalonate (5·3 g) in ethanol (50 ml) was refluxed for 20 hr. On cooling, the product (4 g) crystallized out. It was recrystallized from aq. ethanol; m.p. 103-5° (Found: C, 49·15; H, 4·80; N, 11·89. $C_{15}H_{17}N_3O_4S_2$ requires C, 49·05; H, 4·67; N, 11·44%).

*Reaction of* (IV) *with amines* — (a) *With morpholine* — A mixture of (IV) (6·2 g) and morpholine (3 g) was heated at 100° for 1 hr. After removal of the excess morpholine *in vacuo*, the residue was dissolved in benzene and chromatographed on an alumina column. The benzene eluate (150 ml) on evaporation gave the amidine (VII), which was recrystallized from ethyl acetate-hexane; yield 1·8 g; m.p. 84-86° (Found: C, 48·86; H, 4·72; N, 18·91. $C_{12}H_{14}N_4OS_2$ requires C, 48·98; H, 4·80; N, 19·04%).

(b) *With pyrrolidine* — A mixture of (IV) (5·5 g) and pyrrolidine (2·1 g) was heated at 100° for 1 hr. Work-up as before gave the amidine (1·8 g), crystallized from ethyl acetate-hexane; m.p. 78-79° (Found: C, 52·06; H, 5·24; N, 19·86. $C_{12}H_{14}N_4S_2$ requires C, 51·79; H, 5·07; N, 20·14%).

(c) *With N-methylpiperazine* — A mixture of (IV) (6·2 g) and N-methylpiperazine (3·3 g) was heated at 100° for 1 hr. Excess base was removed *in vacuo*. Toluene (10 ml) was added and again distilled off. The residue was taken in ethyl acetate and washed several times with water. The organic layer was dried, evaporated and the residue crystallized from ethyl acetate-hexane to give (III) (2·7 g); m.p. and m.m.p. 171-3°.

*Diethyl 3-[1,1-dioxido-(1,2)-benzisothiazolyl]aminomethylenemalonate* (VIII)* — A mixture of 3-amino-(1,2)-benzisothiazole-1,1-dioxide (4 g) and diethyl ethoxymethylenemalonate (6 g) was heated at 200° for 1 hr. The product was digested with hexane and then ethanol. The insoluble solid was chromatographed on silica. Elution with a mixture of benzene and chloroform (2:1) gave (VIII) (0·8 g), recrystallized from $CHCl_3$-hexane; m.p. 171-3° (Found: C, 51·48; H, 4·54; N, 8·15. $C_{15}H_{16}N_2O_6S$ requires C, 51·14; H, 4·58; N, 7·95%).

*Reaction of* (VIII) *with morpholine* — A mixture of (VIII) (0·15 g) and morpholine (3 g) was heated at 100° for 1 hr. The product was digested with hexane and crystallized from THF-hexane to give 3-morpholino-(1,2)-benzisothiazole-1,1-dioxide (IX; 0·7 g); m.p. 221-3° (Found: C, 51·92; H, 5·06; N, 10·92. $C_{11}H_{12}N_2O_3S$ requires C, 52·38; H, 4·80; N, 11·11%).

The compound was identical with the product obtained by heating *pseudo* saccharin chloride with morpholine (100°, 1 hr).

## Acknowledgement

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## References

1. Podesva, C., Kohan, G. & Vagi, K., *Can J. Chem.*, **47** (1969), 489.
2. Rajappa, S., Akerkar, A. S. & Iyer, V. S., *Indian J. Chem.*, **7** (1969), 103.

*This experiment was performed by Shri S. R. Mehta.