Tetrahedron. Vol. 26, pp. 3069 to 3071. Pergamon Press 1970. Printed in Great Britain

REACTION OF HYDRAZINE WITH SUBSTITUTED AMINOMETHYLENEMALONATES*

REARRANGEMENT OF MICHAEL ADDUCT TO GIVE TRIAZOLES AND PYRAZOLE.

C. M. GUPTA, A. P. BHADURI, N. M. KHANNA
Central Drug Research Institute, Lucknow, India

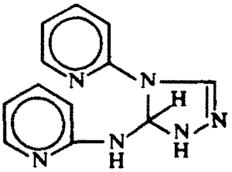
(*Received in the UK* 4 *March* 1970; *Accepted for publication* 25 *March* 1970)

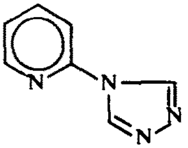
Abstract—Michael reaction of diethyl (substituted amino)-methylenemalonate with hydrazine hydrate gave either 4-substituted-1,2,4-triazoles or 4-carbethoxy-5-hydroxy 4H-pyrazole, depending on the nature of the leaving group in the initially formed adduct.

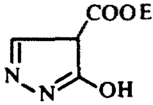
REACTION of diethyl (substituted amino) methylenemalonate with hydrazine has revealed interesting rearrangement reactions which are reported in this paper.

R.NH.CH=C(COOEt)$_2$

I: R = 2-Pyridyl
II: R = 3-Pyridyl
III: R = Phenyl
IV: R = *p*-Tolyl
V: R = 2-Pyrazinyl
VI: R = N-Phenylpiperazino


VII


VIII


IX

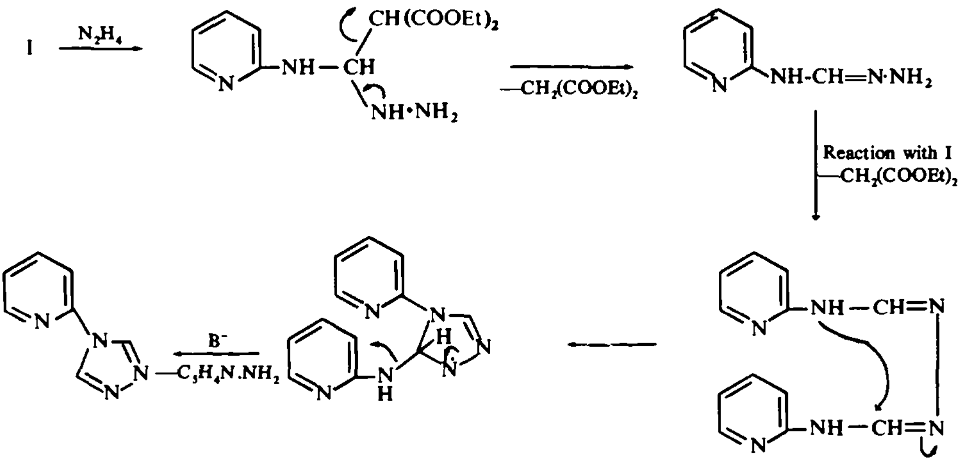
Treatment of diethyl (2-pyridylamino)methylenemalonate (I) prepared according to Lappin[1] (NMR in CDCl$_3$; NH, d at 0·2 τ, $>\text{CH}{=}\text{C}<$ d at 1·39 τ, J = 11 c/s and after deuterium exchange $-\text{CH}{=}\text{C}<$ at 1·39 τ) with hydrazine hydrate at room temperature yielded a crystalline compound (A), mol. formula $C_{12}H_{12}N_6$, mp. 135° (M^+ 240) together with diethylmalonate and an unidentifiable gummy residue. The same reaction in refluxing ethanol gave a different crystalline compound (B), mol. formula $C_7H_6N_4$, m.p. 165° (M^+ 146). Compound A could be transformed into B by heating A at its m.p. for 30 min, by heating with Ac$_2$O, or by treatment with a strong base. The UV spectrum of B showed λ_{max} at 226 and 228 mμ and the IR spectrum did not reveal the presence of NH or carbonyl function. NMR spectrum of B showed a singlet for two protons at 0·99 and four aromatic protons at 1·39–2·72 τ. Based on these considerations B was considered to be 4-(α-pyridyl)-1,2,4-triazole (VIII). Its structure was proved by mixed m.p., superimposable UV and IR spectra with an authentic sample prepared[2] by reacting 2-aminopyridine with diformyl hydrazine at 165°.

---

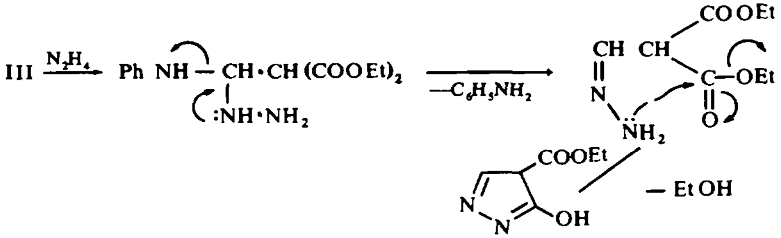
* Communication No. 1492 from Central Drug Research Institute, Lucknow.

The similarity of the mass spectrum of A and VIII suggested A to be a triazole derivative. The mass spectrum of A showed peaks at *m/e* 146 (M^+-2-aminopyridine), *m/e* 119 (*m/e* 146-HCN) and at *m/e* 94 (2-aminopyridine). Since no peak at *m/e* 94 was observed in the mass spectrum of VIII, compound A may be considered as 2-aminopyridyl derivative of VIII. This was further supported by its NMR spectrum (2 NH, broad hump at 0·29 τ; 1 CH, m, at 1·1 τ; 4β protons of pyridine at 3·0 τ; 2 γ protons of pyridine at 2·32 τ and 3 CH, m, at 1·8 τ).

Based on these facts compound A was identified as 4(α-pyridyl)-5-(2-aminopyridyl)-1,5-dihydro-1,2,4-triazole (VII). The probable mechanism by which VII and VIII were formed may be depicted as follows:



In order to ascertain whether this reaction could provide a convenient route for the syntheses of 4,5-disubstituted-1,5-dihydro-1,2,4-triazole III was reacted with hydrazine hydrate in methanol. The reaction, however, did not proceed at room temperature but in refluxing ethanol, III gave a crystalline compound (C) m.p. 178°. Compound C unlike VII or VIII showed the presence of an ester at 1735 cm^{-1} and a hydrogen bonded OH at 3200 cm^{-1} in the IR spectrum. NMR spectrum indicated the prescence of one carbethoxy group and the absence of any aromatic proton. Such a situation would arise only if diethylmalonate was not eliminated from the Michael adduct. It is probable that the reaction could have proceeded according to the scheme below and would give rise to 4-carbethoxy-5-hydroxy-4H-pyrazole (IX).



The structure of IX was finally proved through mixed m.p., superimposable UV and IR spectra with an authentic sample prepared according to Ishimaru.[3] The formation of triazole from I and pyrazole from III led to a study of the reaction of hydrazine with II, IV, V and VI respectively. It was found that appropriately 4-substituted-1,2,4-triazoles were obtained from II and V while compounds IV and VI gave IX.

While no definite reason could be ascribed for the elimination of diethylmalonate in some cases and the amines in the others, it appeared likely that the N atom of diethyl(substituted amino)-methylenemalonate in I, II and V had either double bond or partial double bond character whereas in III, IV and VI the N atom had predominantly Sp^3 character which probably decided the course of the elimination reaction. Since sp^3 nitrogen is a better leaving group than a sp^2 nitrogen, the elimination of diethylmalonate was preferred in I, II and V while the elimination of the amine was more favourable in III, IV and VI.

EXPERIMENTAL

All m.ps. are uncorrected. IR and UV spectra were recorded on Perkin-Elmer 337 and 202 spectrophotometers respectively. The NMR spectra were recorded on Varian A60D model, using TMS as an internal standard.

Diethyl (2-*aminopyrazinyl*) *methylenemalonate* (V). A mixture of 3-aminopyrazine-2-carboxylic acid (2·8 g) diethyl ethoxy methylenemalonate (4·5 ml) was heated at 160-80° for 2 hr, during which decarboxylation was complete. After cooling the residue was triturated with MeOH, filtered and crystallized from MeOH m.p. 121°, yield 3·2 g. (Found: C, 54·40; H, 5·73; N, 15·60; $C_{12}H_{15}N_3O_4$ required: C, 54·34; H, 5·66; N, 15·84%. Other diethyl (substituted amino) methylenemalonates were prepared according to Lappin.[1]

4(α-*Pyridyl*)-5-(2-*aminopyridyl*)-1,5-*dihydro*-1,2,4-*triazole*(VII). A soln of I (1·4 g) in MeOH (10 ml) was treated with $N_2H_4H_2O$ (0·5 ml, 80%) and left at room temp for 18 hr. The crystalline solid was filtered off and crystallized from aqueous MeOH, m.p. 135°, yield, 0·5 g. (Found: C, 60·15; H, 5·18; N, 35·19; $C_{12}H_{12}N_6$ requires: C, 59·97; H, 5·14; N, 34·72%).

4-(α-*Pyrazinyl*)-1,2,4-*triazole*. A soln of V (2·5 g) in EtOH (15 ml) was refluxed with $N_2H_4 . H_2O$ (0·6 ml, 80%) for 4 hr. After removal of the solvent, the residue was crystallized from $CHCl_3$-light petroleum, m.p. 175–176°, yield—0·8 g. (Found: C, 48·83; H, 3·74; N, 48·01; $C_6H_5N_5$ requires: C, 48.99; H, 3·46; N,47·61%).

Reaction of III, IV *and* VI *with* $N_2H_4 . H_2O$. An equimolar mixture of III, IV or VI and $N_2H_4 . H_2O$ was refluxed in EtOH for 4 hr. After removal of the solvent, the residue was treated with 10% HCl aq, filtered and crystallized from water to give IX, m.p. 180° (lit. 180–181°).

Acknowledgement—Thanks are due to Shri J. Saran and his associates for microanalysis.

REFERENCES

[1] G. R. Lappin, *J. Am. Chem. Soc.* **70**, 3348 (1948)
[2] R. H. Wiley, A. J. Hart, *J. Org. Chem.* **18**, 1368 (1953)
[3] T. Ishimaru, *Chem. Abstr.* 51, 17893 (1957)