A New Triazaphenothiazine Ring with Tranquilizing Activity

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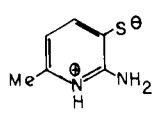
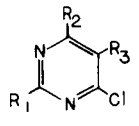
Sir:

Phenothiazine and its derivatives have been widely studied and may be used in several different ways (3-5). The major applications are in medicine where they constitute the important class of phenothiazine drugs (6) and as phenothiazine dyes, a major group of sulphur dyes (7). In spite of their wide applicability and extensive studies on them, only one triazaphenothiazine ring has been reported in the literature (8) out of a variety of 24 possible structural isomers (9). In view of the remarkable antipsychotic action of prothipendyl, the 1-azaphenothiazine analogue of promazine (4,10), we have now synthesized and tested some derivatives of a new phenothiazine ring with annular nitrogen atoms in the active sites, 1-, 3- (11) and 9-positions (12).

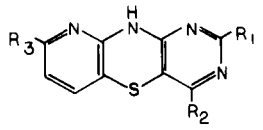
In these reactions, 2-amino-6-methylpyridine was converted to the 3-thiocyanato derivative (13) followed by base-catalysed hydrolysis and acidification. The hydrolysis product is a greenish yellow solid melting at 245°, soluble in sodium hydroxide but insoluble in acid. Elemental analysis and low resolution mass spectrometry were correct for $C_6H_8N_2S$; λ max (methanol): 256 (log ε 3.85), 302 nm (log ε 3.56), ν max (potassium bromide disc): 3340 d (2-NH_2), 3197 (ring NH), 1667 (C=NH), 1227 (2-NH_2) and 841 cm^{-1} (4-CH and 5-CH out-of-plane deformation). The solubility in base, insolubility in acid and the absence of weak SH signal at 2550 cm^{-1} even in concentrated solutions are strong evidence for the zwitterionic character. The dipolar structure, I, was therefore assigned to this product. Further evidence of structure was provided by the nmr spectrum which showed that one of the amino group protons had very different chemical shift from the other two in agreement with structure (I); δ 2.53 s (6-CH_3), 6.78 d (J = 9.2 Hz) (5-CH), 7.80 b (2-NH_2), 7.94 d (J = 9.2 Hz) (4-CH), 8.27 b (1-NH).



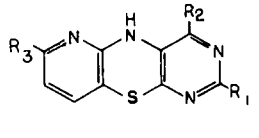
I



II, R_1 = R_2 = OMe, R_3 = Br
V, R_1 = H, R_2 = NH_2, R_3 = NO_2



III



IV

Reaction of compound I with 5-bromo-4-chloro-2,6-dimethoxypyrimidine (II) in acidic medium led to a white product of molecular formula $C_{12}H_{12}N_4O_2S$, m.p. > 300°, in 68% yield.

Anal. Calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.18; H, 4.35; N, 20.29; S, 11.60. Found: C, 51.79; H, 4.19; N, 20.46; S, 11.51.

From a study of the uv, ir, nmr and mass spectra, this product was formulated as 2,4-dimethoxy-8-methyl-1,3,9-tirazaphenothiazine (III) (R_1 = R_2 = OMe, R_3 = CH_3); λ max (methanol): 221 (log ε 3.86), 250 (log ε 3.77) and 283 nm (log ε 3.86). The product, thus, gave the maximum absorption band at 250 nm, characteristics of phenothiazinoid systems; ν max (potassium bromide disc): 3400 (10-NH), 1650 (NH deformation), 1200 (C-O-C linkage), 830 cm^{-1} (6-CH, 7-CH); nmr spectrum (DMSO-d_6): δ 2.33 s (8-CH_3), 3.63 s (4-OCH_3), 3.68 s (2-OCH_3), 6.37 d (J = 8.2 Hz), (7-CH), 6.30 b(10-NH), 7.40 d (J = 8.2 Hz) (6-CH); mass spectrum m/e (rel intensity): 94 (100), 112 (29), 180 (5), 261 (5), 262 (20), 276 (M+, 9). A more diffuse nmr signal and a stronger intramolecular hydrogen bonding is expected from the alternative structure IV due to chelation between the oxygen of the methoxy group and the 10-NH proton leading to a 5-membered ring of high stability (14). The acid catalysed reaction of compound I with 4-amino-6-chloro-5-nitro-pyrimidine (V) gave a product of molecular formula $C_{10}H_9N_5S$ melting above 300°.

Anal. Calcd. for $C_{10}H_9N_5S$: C, 51.95; H, 3.89; N, 30.31; S, 13.86. Found: C, 52.08; H, 3.70; N, 30.14, S, 14.00; ν max (Nujol): 3390; 3100, 1650, 1603, 1250, 1180, 1136, 1019, 980, 895, 794 cm^{-1}; δ (DMSO-d_6) (15): 8.20 b (4-NH_2), 7.60 d (J = 9.0 Hz) (6-H), 7.58 s (2-H), 6.69 d (J = 9.0 Hz) (7-H), 7.63 s (8-CH_3). This product failed to give the 1,10-diazole structure characteristic of *o*-aminodiarylamines (16-18). On the basis of this

evidence, this product is therefore 4-amino-8-methyl-1,3,9-triazaphenothiazine (III, R_1 = H, R_2 = NH_2, R_3 = CH_3) rather than the 1,6,8-triazaphenothiazine structure. This reaction confirms the 1,3,9-triazaphenothiazine structures assigned to the products of these reactions.

Preliminary pharmacological studies with mice and rats show that these 1,3,9-triazaphenothiazines have appreciable tranquilizing activity when compared to chlorpromazine. Using doses only slightly higher than that of chlorpromazine, 4-amino-8-methyl-1,3,9-triazaphenothiazine (III, R_1 = H, R_2 = NH_2, R_3 = CH_3) produced a significant decrease in spontaneous motor activity and the rate of respiration within 30 minutes. It also potentiates hexobarbital-sodium sleeping time and is more likely to act directly on the central nervous system unless it acts as an excretory inhibitor. All the derivatives of 1,3,9-triazaphenothiazine tested caused a decrease in the body temperature in some cases by as high as 1.9° compared to 0.8° in chlorpromazine.

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