

Studies in the Diazine System II. A New Synthesis of 1-Alkyl-6(1*H*)-pyridazinones (1)

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In the search for chemical agents effective against drug resistant strains of malaria plasmodia, we have studied the preparation of 1-(ω -dialkylaminoalkyl)-6(1*H*)-pyridazinones. During the program a series of compounds incorporating several ring substituents was contemplated. The preparation of 1-dialkylaminoethyl-4,5-dichloro-6(1*H*)-pyridazinones was undertaken first, because the 4-halo substituent in such compounds is amenable to nucleophilic substitution.

The reaction of alkyl halides with 6(1*H*)-pyridazinone (I) was reported by Overend (3). The usual conditions for the reaction are strong base in refluxing methanol. When these conditions were used to react diethylaminoethylchloride with 4,5-dichloro-6(1*H*)-pyridazinone (III), an unexpected product (IV) was obtained. The expected *N*-substitution had occurred, but in addition, the chlorine atom at position 4 was replaced by the methoxyl group. This was surprising, because several previous attempts to

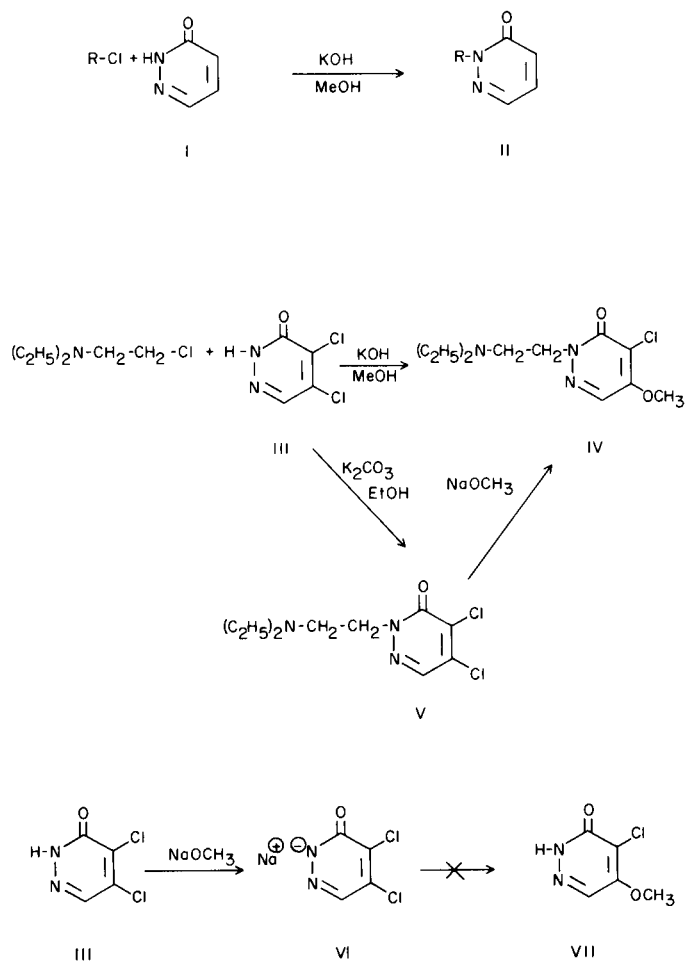
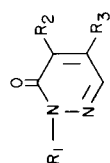


Figure 1

TABLE I



No.	R ₁	R ₂	R ₃	Salt	M.P. (°C)	Yield (%)	Empirical Formula	Calculated %C %H %N	Found %C %H %N	Method
IV	(C ₂ H ₅) ₂ N-CH ₂ -CH ₂ -	Cl	OCH ₃	-	60-61	27.5	C ₁₁ H ₁₈ ClN ₃ O ₂	50.86 7.00 16.18	50.75 7.09 15.87	A,C
V	(C ₂ H ₅) ₂ N-CH ₂ -CH ₂ -	Cl	Cl	HCl	>300	21.7	C ₁₀ H ₁₆ Cl ₃ N ₃ O	39.95 5.37 14.00	39.73 4.99 13.84	B
IX	(CH ₃) ₂ N(CH ₂) ₃ -	Cl	OCH ₃	2H ₂ O	187.9	69	C ₁₀ H ₂₀ ClN ₃ O ₄	42.63 7.16 14.91	42.89 7.02 14.88	C
X	(CH ₃) ₂ N(CH ₂) ₃ -	Cl	Cl	HCl·2H ₂ O	110-12	16.6	C ₉ H ₁₈ Cl ₃ N ₃ O ₃	33.50 5.62 13.03	33.43 5.57 12.88	B
XI	(CH ₃) ₂ N-CH ₂ -CH- CH ₃	Cl	OCH ₃	4H ₂ O	151-3	15	C ₁₀ H ₂₄ ClN ₃ O ₆	37.79 7.61 13.22	37.78 8.36 13.07	A
XII	(CH ₃) ₂ N-CH ₂ -CH- CH ₃	Cl	Cl	HCl	>300	12.2	C ₉ H ₁₄ Cl ₃ N ₃ O	37.72 4.92 14.66	37.95 5.13 14.45	B

replace the 4-chlorine atom in the starting pyridazinone with methoxide ion had failed.

Apparently, these reactions failed because the sodium salt of the acidic cyclic amide (VI) was formed. In the salt form, the pyridazinone ring is negatively charged and deactivated for nucleophilic substitution.

The same intermediate (VI) should be formed in the reaction with an alkyl halide, but in this case, salt formation renders the ring nitrogen nucleophilic. The strong base thus acts as a catalyst for nucleophilic attack by the ring on the halide. However, once the substitution reaction has been completed, salt formation is no longer possible and the ring is no longer deactivated for nucleophilic attack. Under the strongly basic conditions of the reaction mixture the chlorine at position 4 should be rapidly replaced by methoxide ion, giving the product obtained (IV).

A proof of this proposed pathway would be afforded by the isolation of a 1-(ω-dialkylaminoalkyl)-4,5-dichloro-6(1*H*)-pyridazinone (such as V), the type of compound we had originally set out to prepare. An example of the intermediate (V) was isolated when the reaction shown was carried out in absolute ethanol with anhydrous potassium carbonate as catalyst. Conversion of this intermediate to the corresponding 4-methoxy derivative completed the proof of the course of the reaction.

The *N*-substitution reaction has not previously been successful under such mild conditions. Apparently, its success in this case is due to the activation of the ring chlorine atoms. The corresponding reaction with the unsubstituted 6(1*H*)-pyridazinone (I) fails under these conditions. However, the unsubstituted 1-dialkylaminoalkyl-6(1*H*)-pyridazinones are available by hydrogenation of the dichloro intermediate.

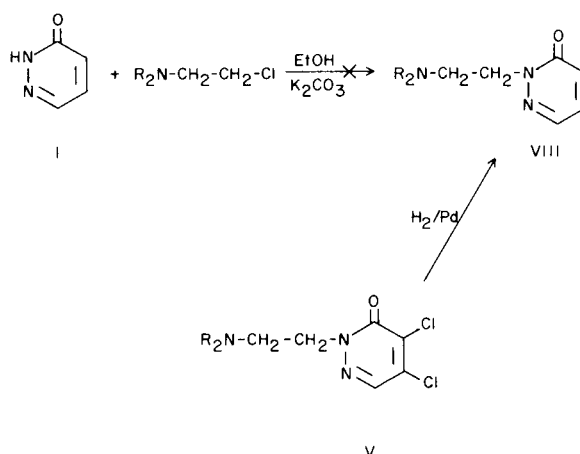


Figure 2

The mild reaction conditions have proven to be extremely useful for the preparation of longer chain dialkylaminoalkyl compounds. Many of the longer chain dialkylaminoalkyl halides rearrange and polymerize when treated with strong base (4), and they generally fail to react with pyridazinones under the usual conditions. But with anhydrous potassium carbonate as the catalyst, excellent yields of these compounds were obtained. No decomposition of the aminohalides was observed.

The compounds prepared in this study together with some of their physical properties are shown in Table I. Compounds II, IV and X were submitted to the Walter Reed Army Institute of Research for screening as anti-malarial agents, but were toxic to mice. The other compounds in Table I were not submitted for testing.

EXPERIMENTAL

Method A.

5-Chloro-1-(β -diethylaminoethyl)-4-methoxy-6(1*H*)-pyridazinone (IV).

To a boiling, well stirred solution of 2.5 g. (0.04 mole) of potassium hydroxide in 100 ml. of methyl alcohol was added 3.3 g. (0.02 mole) of 4,5-dichloro-6(1*H*)-pyridazinone. To this mixture, 2.75 g. (0.02 mole) of 2-diethylaminoethyl chloride dissolved in 25 ml. of methyl alcohol was added dropwise over 20 minutes. The whole was stirred, heated at reflux for 2 hours and stirred at room temperature for 18 hours. The mixture was diluted with an equal volume of water and steam distilled. The residue was extracted with ether and the extract dried (magnesium sulfate) and evaporated. The oily residue crystallized on standing and was recrystallized from petroleum ether, giving 1.45 g. (27.4%) of the product, m.p. 60-61°.

Method B.

4,5-Dichloro-1-(β -diethylaminoethyl)-6(1*H*)-pyridazinone Hydrochloride (V).

To a solution of 4.25 g. (0.025 mole) of 4,5-dichloro-6(1*H*)-pyridazinone in 100 ml. of ethyl alcohol was added 10.5 g. (0.075 mole) of potassium carbonate. This mixture was heated to reflux and stirred vigorously while 3.4 g. (0.025 mole) of 2-dimethylaminoethyl chloride in 25 ml. of ethyl alcohol was added dropwise over 30 minutes. The whole was stirred and heated at reflux for 48 hours. The solvent was evaporated and the residue was taken up in tetrahydrofuran, filtered, and dried (magnesium sulfate). The solution was treated with anhydrous hydrogen chloride, giving the product as a white crystalline solid. It was recrystallized from isopropyl alcohol, yield: 1.6 g. (21.7%), m.p. > 300°.

Method C.

5-Chloro-1-(β -diethylaminoethyl)-4-methoxy-6(1*H*)-pyridazinone (IV).

To a well stirred solution of 0.55 g. (0.01 mole) of sodium methoxide in 25 ml. of methyl alcohol, 1.0 g. (0.0033 mole) of 4,5-dichloro-1-(β -diethylaminoethyl)-6(1*H*)-pyridazinone hydrochloride (V) was added. The whole was stirred and heated at reflux for 20 hours. The cooled solution was diluted with an equal volume of water, and the methyl alcohol was removed *in vacuo*. The aqueous solution was extracted with ethyl ether, and the extracts dried (magnesium sulfate) and evaporated. The residue crystallized on standing and was recrystallized from petroleum ether, giving 0.63 g. (73%) of a product identical in all respects with Compound IV obtained by Method A.

REFERENCES

- (1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-3019. Antimalarial testing results are pending.
- (2) Present address: Placer Union High School District, Auburn, California.
- (3) W. G. Overend, L. M. Turton, and L. F. Wiggins, *J. Chem. Soc.*, 3500 (1950).
- (4) German Patent No. 1,040, 503, Oct. 9, 1958.

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