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PYRIMIDINES FROM ALKYLMALONIC ESTERS AND AROMATIC AMIDINES.[1]

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The condensation of dialkylmalonic esters with guanidine is well known because of its application in some of the processes for the manufacture of veronal. Aside from guanidine,[2] dicyanodiamide[3] and guanyl-urea (dicyano-diamidine)[4] none of the amidines appear to have been condensed with alkylmalonic esters.

In the synthesis of the malonyl-guanidines it has been assumed that the two primary amino groups of guanidine condense with the carbethoxyl groups of the malonic ester, forming substituted hexahydro-pyrimidines. It is not unlikely, however, that the tautomeric form may exist, representing a condensation in which the imino group has reacted instead of one of the amino groups, with formation of a tetrahydro-pyrimidine. The close analogy between urea, thio-urea and guanidine supports the first assumption. In the case of guanyl-urea, it is known that the condensation product is a mixture of tautomers.

Ethyl malonate has been condensed with benzamidine by Pinner.[5] In his first attempt Pinner obtained only the acid malonate of benzamidine. In his later work, he found that a condensation took place in the presence of aqueous alkali, but the yield was poor (10%) because of the rapid saponification of the ester. With sodium ethylate, however, the condensation occurred at ordinary temperature giving in 2 days a 50% yield of 2-phenyl-4,6-diketo-tetrahydro-pyrimidine. Pinner states that a longer time, up to 6 weeks, did not increase the yield.

Although substituted malonic esters have not been condensed with amidines, the identical products that should result from such condensations have been prepared in other ways.

Freund and Fleischer[6] prepared 5 5-diethyl-2-methyl-4,6-diketo-tetrahydro-pyrimidine from diethylmalonyl chloride and acetamide. From the intermediate diethylmalonyl-diacetamide first formed, the loss of acetic acid and ring closure gave the above pyrimidine. Remfry[7] prepared several di- and tri-alkyl-diketo-tetrahydro-pyrimidines by condensing alkylmalonamides with alkylmalonic esters. This is an unusual reaction, since the 8-membered ring expected does not form, but instead a loss

[1] Read at the New York meeting of the American Chemical Society, September 9, 1921.

[2] Fischer and Dilthey, *Ann.*, **335**, 352 (1904). Gerngross, *Ber.*, **38**, 3399 (1906). Johnson and Hill, *Am. Chem. J.*, **46**, 537–49 (1911). Karst, *Ber.*, **45**, 3130 (1912). Dox and Yoder, THIS JOURNAL, **43**, 683 (1921). Ger. pat. 189,076 (1907); 231,887 (1911); 235, 802 (1911).

[3] Ger. pat. 158,591 (1905); 165,223 (1905); 175,795 (1906).

[4] Ger. pat. 170,586 (1906); 171,147 (1906); 187,990 (1907).

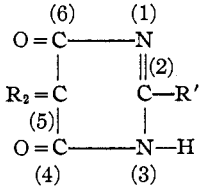
[5] Pinner, *Ber.*, **18**, 763 (1885); **41**, 3517–9 (1908).

[6] Freund and Fleischer, *Ann.*, **379**, 27–36 (1910).

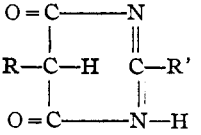
[7] Remfry, *J. Chem. Soc.*, **99**, 610–25 (1911).

of carbon dioxide occurs and a substituted pyrimidine results. The products he obtained correspond to derivatives that should result from direct condensation of alkylmalonic esters with several aliphatic amidines. Burrows and Keane[8] condensed diethylmalonamide with benzaldehyde and obtained 5,5-di-ethyl-2-phenyl-4,6-diketohexahydro-pyrimidine. This substance would be the reduction product of the condensation product from diethylmalonic ester and benzamidine, by the simple addition of two hydrogens at the double linkage.

The experiments herein described were undertaken primarily for the purpose of studying the physiological properties of the tetrahydro-pyrimidines resulting from condensation of dialkylmalonic esters with aromatic amidines. Incidentally, it was discovered that the mono-alkyl derivatives, in contrast to the di-alkyl derivatives, are colored, suggesting a tautomeric structure. A number of the mono derivatives were therefore included among our preparations. We have then two series. Disregarding tautomeric rearrangements the formulas would be



(I). Colorless



(II). Colored

Experimental.

Our first experiments, in which we attempted to condense benzamidine with various dialkylmalonic esters purchased from a reliable source, caused us some perplexity. Beautifully crystalline, bright yellow, insoluble products were obtained which, however, showed the nitrogen content of the mono-alkyl instead of the expected di-alkyl derivatives. It was only when we came to work up the mother liquors that we obtained the colorless di-alkyl derivatives. In the case of ethyl dibutylmalonate we did not succeed in obtaining the dibutyl pyrimidine until after the ester had been subjected to a second alkylation with butyl bromide and sodium ethylate. In fact, of the dialkylmalonic esters purchased by us, the only one which did not give an appreciable quantity of the yellow mono-alkyl pyrimidine was ethyl dibenzylmalonate. The dialkylmalonic esters which we prepared ourselves were comparatively free from the mono derivative, yet in several instances its presence was indicated by the yellow color of the crude condensation product.

This experience recalls the observation of Fischer and Dilthey[9] that the esters of dialkylmalonic acids invariably contain esters of the corresponding monoalkylmalonic acids unless special precautions are taken to remove

[8] Burrows and Keane, *J. Chem. Soc.*, **91**, 269–71 (1907).

[9] Fischer and Dilthey, *Ber.*, **35**, 844–56 (1902).

the latter. In the case of ethyl diethylmalonate this impurity ordinarily amounts to 7–8%. The boiling points lie too closely together for a satisfactory separation by fractionation. The striking difference in the rate of amide formation when the ester is treated with aqueous ammonia is recommended by Fischer and Dilthey as a test for the presence of mono derivative and as a means of removing the latter. Meyer[10] showed later that this difference in the rate of amide formation is less noticeable with methyl esters than with ethyl esters, except in the case of diethyl-malonic acid. We believe that the color of the condensation product with benzamidine is an equally delicate test for the presence of monoalkylmalonic ester.

The separation of mono- from di-alkyl pyrimidines resulting from the condensation of the mixed malonic esters with aromatic amidines is, however, a simple matter. The difference in solubility is very great. The yellow mono-alkyl derivative is practically insoluble in all neutral solvents. It may be purified by dissolving in alkalies and reprecipitating it with acids, or it may be crystallized from glacial acetic acid in which it is sparingly soluble, or precipitated from this solution by dilution with water. The white di-alkyl pyrimidine, on the other hand, crystallizes readily from alcohol.

Benzamidine condenses more readily with alkyl malonic esters than does urea. For this reason, it is unnecessary, and in fact inadvisable, to use autoclave temperatures. In several experiments in which the condensations were performed at 110° the yields were very poor. A strong odor of benzonitrile was noticed, indicating a decomposition of the amidine. Our best yields were obtained at 70–75°. An excess of sodium was also found to increase the yield.

For purposes of comparison the unsubstituted malonic ester was also condensed with benzamidine, and likewise with acetamidine. Using an excess of sodium ethylate and a temperature of 105° we obtained a yield of 81% as compared with Pinner's 50% yield. The substance showed the properties of Pinner's 2-phenyl-4,6-diketo-tetrahydro-pyrimidine. We noted in addition that its behavior toward aromatic aldehydes is similar to that of barbituric and thio-barbituric acids.[11] In hydrochloric acid solution it immediately develops a color and finally an insoluble precipitate on the addition of an aromatic aldehyde. Benzaldehyde, cinnamic aldehyde, anisic aldehyde and piperonal all gave derivatives whose color varied from yellow to brick-red. These precipitates were soluble in alkalies, but insoluble in all other solvents and difficult to obtain sufficiently pure for analysis. In acetic acid solution no reaction occurs until a few drops of hydrochloric acid are added.

[10] Meyer, *Ber.*, **39**, 198–200 (1906).

[11] Dox and Plaisance, THIS JOURNAL, **38**, 2164–6 (1916).

The procedure followed in the preparation of the alkyl substituted pyrimidines was in the main the same throughout; hence a single protocol for each series will suffice by way of illustration. The amidines were prepared from the respective nitriles through the imido-ether salts.

5,5-Diethyl-2-phenyl-4,6-diketo-tetrahydro-pyrimidine.—To a solution of 4.5 g. of sodium in 75 cc. of absolute alcohol, 9 g. of benzamidine hydrochloride and 10 g. of carefully purified ethyl diethylmalonate were added. The mixture was heated for 7 hours at 70°. The alcohol was partially removed by a current of dry air and the residue acidified with a slight excess of conc. hydrochloric acid. After removal of the precipitated sodium chloride, the solution was further concentrated on the steam-bath. The addition of water caused the product to separate in white needles. The yield was 5 g. The substance was recrystallized from dil. acetic acid. It will be noted in this instance that the yellow color due to the formation of mono-alkyl derivative was not observed. This we attribute to the fact that the ethyl diethylmalonate had been given a second treatment with ethyl bromide and sodium ethylate, and the usual impurity of ethyl monoethylmalonate was not present.

5-Benzyl-2-phenyl-4,6-diketo-tetrahydro-pyrimidine.—To a solution of 1.5 g. of sodium in 20 cc. of absolute alcohol, 2.8 g. of benzamidine

TABLE I

4,6-DIKETO-TETRAHYDRO-PYRIMIDINES

Nos. 1-4 and 14-21 were white; the others were yellow in color

	Substituents		Melting point °C.	Nitrogen Calc. %	Nitrogen Found %	%	Yield %
	5-carbon	2-carbon					
1.	.....	methyl	300+	22.22	22.08	22.15	62
2.	phenyl	methyl	300+	13.86	13.45	13.31	70
3.	benzyl	methyl	300+	12.96	12.70	12.91	85
4.	.....	phenyl	300+	14.89	14.43	14.63	81
5.	methyl	phenyl	300+	13.86	13.57	13.65	..
6.	ethyl	phenyl	300+	12.96	12.92	12.78	..
7.	allyl	phenyl	288–9	12.28	12.27	12.34	70
8.	butyl	phenyl	296–7	11.47	11.34	11.41	44
9.	*iso*amyl	phenyl	300+	10.85	10.71	10.99	45
10.	benzyl	phenyl	300+	10.07	10.01	9.87	100
11.	dimethyl	phenyl	263	12.28	12.39	12.53	61
12.	ethyl	*p*-tolyl	300+	12.17	11.88	12.23	..
13.	ethyl	*p*-ethoxy-phenyl	300+	11.47	11.31	11.15	..
14.	dimethyl	phenyl	184	12.96	12.71	12.64	45
15.	di-ethyl	phenyl	207	11.47	11.37	11.49	44
16.	dipropyl	phenyl	164	10.29	10.47	10.19	45
17.	dibutyl	phenyl	144	9.33	9.27	9.41	..
18.	dibenzyl	phenyl	234	7.61	7.40	7.62	37
19.	di-ethyl	*p*-tolyl	181	10.85	10.80	10.88	40
20.	di-ethyl	*p*-ethoxy-phenyl	165	9.75	9.73	9.65	..
21.	di-ethyl	β-naphthyl	178	9.52	9.45	9.59	59

hydrochloride and 4 g. of ethyl benzylmalonate were added. The mixture was kept at about 40° for 12 hours. It was then acidified with conc. hydrochloric acid, the yellow precipitate collected on a filter and the sodium chloride washed out with water. The crude product weighed 4.5 g. It was insoluble in water and the neutral organic solvents. It dissolved with difficulty in glacial acetic acid from which it was obtained as bright yellow needles on cooling the solution. In mineral acids and alkalies it dissolved to give a colorless solution from which the yellow crystals were again obtained on neutralization.

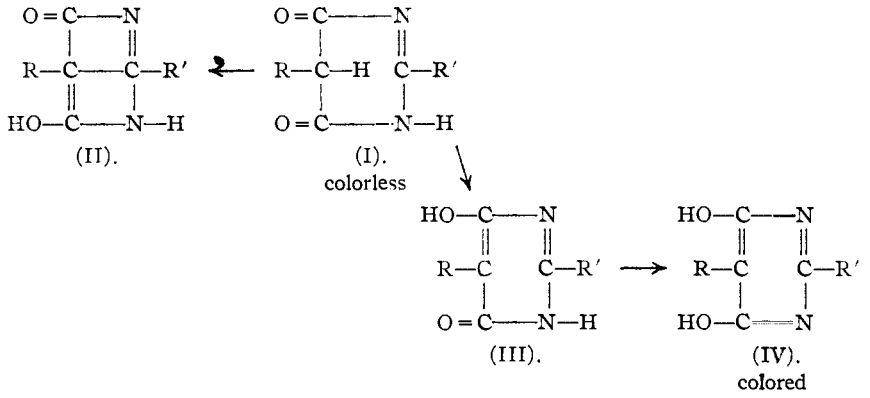
The two series of derivatives which we prepared from mono- and dialkylmalonic esters are listed in the preceding table. In the case of 5-mono-alkyl derivatives where the yield is not stated, the substance was obtained as a by-product accompanying the corresponding di-alkyl derivative.

Discussion.

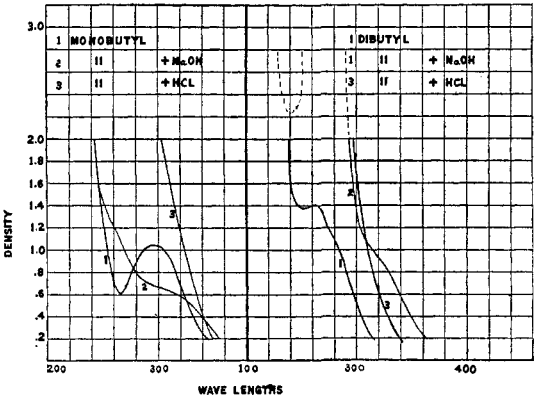
In the foregoing table several pairs of isomers will be noted, of which one is colorless and the other colored. In Nos. 2 and 5 the positions of the methyl and phenyl are simply reversed. Nos. 8 and 15 show isomerism due to an alkyl group in one case, equivalent to two smaller alkyl groups in the other. Nos. 9 and 19 are analogous to the preceding with the additional variation of a methyl group attached in the one case to the 5-alkyl group, and in the other to the 2-aryl.

It will be noted that the 5-mono-alkyl derivatives from the aromatic amidines are all yellow, and with two exceptions do not melt below 300°. Pinner states that his 5-bromo-2-phenyl-4,6-dioxy-pyrimidine was bright yellow in color and melted with decomposition at 320°. Evidently a halogen on the 5-carbon atom is equivalent to an alkyl group. The 5,5-di-alkyl derivatives, on the other hand, are all colorless and melt considerably below 300°. An apparent exception to the color rule is the trimethylene derivative which, however, is a *spiro* compound. The difference in solubility has already been pointed out. The presence of the 2-aryl group appears to be necessary for the manifestation of color in the 5-mono-alkyl series, since corresponding derivatives with methyl in place of the aryl group are colorless. Leaving out of consideration the *spiro* derivative (No. 11), the two criteria which determine color in the 4,6-dioxy-pyrimidines are a 2-aryl group and a 5-hydrogen atom. The latter makes possible a rearrangement into a tautomeric enolic form with 3 double linkages in the ring.

A hemiquinoid structure (Formula II) does not in itself imply color. Such structure is known where color is absent. Formula III does not account for the color, since a similar structure with 2 alternate double linkages can also be assigned to the 5,5-di-alkyl derivatives which are invariably colorless. Formula IV, therefore, represents the most probable



structure of the colored derivatives. Through the kindness of Dr. H. T. Clarke, of the Eastman Kodak Company, the absorption spectra of typical yellow and colorless derivatives were determined by means of the spectrophotometer. The curves below, where density of absorption is plotted against wave length, were obtained by using a 1cm. layer of 0.00005 *M* solutions in methyl alcohol. The monobutyl derivative shows a decided band (Curve I) in the violet, which disappears on the addition of a few



drops of alkali or acid (Curves II and III). The dibutyl derivative shows only an extension in the region beyond the visible. The effect of alkali in this case is to produce a band corresponding in position to the extension shown by the pure substance. With both derivatives the effect of acid is a strong general absorption nearer to the visible.

Summary.

Alkylmalonic esters condense readily with aromatic amidines, the monoalkylmalonic esters yielding insoluble yellow pyrimidine derivatives, and the dialkylmalonic esters soluble, colorless derivatives. The color may perhaps be explained on the basis of tautomeric rearrangement.

DETROIT, MICHIGAN.