Summary

It was expected that the substitution of a methyl group in the 2′-position of 1′-naphthoyl-2-benzoic acid would prevent the formation of an anthraquinone on subjecting this substance to condensation in the sodium aluminum chloride melt. It was found, however, that two isomeric methyl-1,2-benzanthraquinones are produced and a study has been made of the rearrangement obviously involved in the course of the reaction. Through the identification of the methylbenzanthraquinones and a study of the condensation of various dimethyl-1′-naphthoyl-2-benzoic acids it has been found that the rearrangement involves the migration of the phthalic acid residue to a β-position of the originally unsubstituted ring.

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RESEARCHES ON PYRIMIDINES. CXXX. SYNTHESIS OF 2-KETO-1,2,3,4-TETRAHYDROPYRIMIDINES

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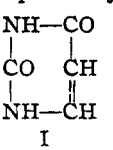
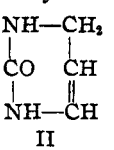
This paper is presented as a preliminary contribution dealing with methods of synthesis and the chemistry of 2-keto-1,2,3,4-tetrahydropyrimidine compounds. The structural relationship between uracil and the mother substance of such a series (acroleinharnstoff) is expressed by formulas I and II, respectively. Theoretically the pyrimidine II should



I



II

be formed by the action of acrolein on urea, but, thus far, all attempts to prepare this compound by interaction of these reagents have been unsuccessful.[2,3,4]

A practical procedure for preparing derivatives of this pyrimidine II was first described by Biginelli[5] in 1893. This is based on that investigator's discovery that an aldehyde will combine with a β-keto ester and urea in alcohol solution with smooth formation of a tetrahydropyrimidine. With benzaldehyde and ethyl acetoacetate, for example, he was able to

[1] Squibb and Sons Research Fellows in Organic Chemistry, 1931–1932.

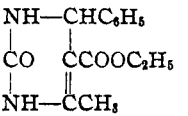
[2] Schiff, *Ann.*, **151**, 203 (1869); *Ber.*, **15**, 1393 (1882).

[3] Leeds, *Ber.*, **15**, 1159 (1882).

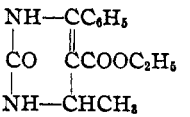
[4] Lüdy, *Monatsh.*, **10**, 300 (1889).

[5] Biginelli, *Gazz. chim. ital.*, **23**, 360 (1893); *Atti. accad. Lincei*, [5] **3**, 195 (1894); *Chem. Zentr.*, **65**, 823 (1894); *Ber.*, **24**, 1317 (1891).

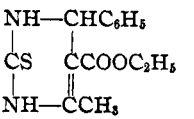
prepare 2-keto-6-methyl-5-carbethoxy-4-phenyl-1,2,3,4-tetrahydropyrimidine III, and he also applied the reaction successfully with several dif-



III



IV



V

ferent aldehyde combinations. Biginelli showed, furthermore, that the same pyrimidine III is also formed by interaction of benzaldehyde with β-carbamidocrotonic ester, by combining benzylidene-diureide with ethyl acetoacetate and by the action of ethyl α-benzalacetoacetate on urea.

Apparently no further attention was paid to the Biginelli condensation until 1929, when Hinkel and Hey[6] took up his work and introduced changes in experimental technique which they considered favorable for the production of dihydropyridines according to the Hantzsch reaction. These investigators did succeeed in demonstrating the formation of dihydropyridines by using Biginelli's reagents, but they found that in every case examined, the main product of the condensation was still a tetrahydropyrimidine derivative as originally formulated by Biginelli. The authors became interested in the chemistry and application of the Biginelli condensation for the following reasons: (a) the necessity of acquiring additional evidence in support of the constitution assigned to the products of reaction described by Biginelli: (b) the need of a clearer conception of the mechanism of the change leading to these pyrimidine formations, and (c) the possible application of the reaction for the synthesis of a large number of new organic substances for pharmacological research, in which constitutional changes of great variety could be incorporated. In fact, this series of pyrimidines offers unusual possibilities for evaluating and determining the influence of definite changes in molecular structure on physiological action.

If Biginelli's conclusion of cyclic structure as represented in formula III is correct, one is compelled to take under consideration also the isomeric forms as represented in formula IV. In tetrahydropyrimidines of this type we are dealing with cyclic allyl constructions and from our past experience it is known that such unsaturated groupings are theoretically prone to isomeric change, in this case with shifting of a double bond in the pyrimidine ring. This interesting question of isomerization is now receiving attention by us, and will be discussed in a future paper. Hinkel and Hey obtained evidence of isomerization when they examined the behavior of thio-urea toward benzaldehyde, ethyl acetoacetate and urea The introduction of a mixture of urea or thiourea, a β-keto ester and an aldehyde together into a common solution like alcohol constitutes an or-

[6] Hinkel and Hey, *Rec. trav. chim.*, **48**, 1280 (1929).

ganic system which presents the possibility of a variety of chemical reactions taking place. It would be predicted, therefore, that different organic combinations would be capable of formation depending upon the experimental conditions employed. Biginelli observed no evidence of the formation of any product except a tetrahydropyrimidine, while Hinkel and Hey working under different conditions report the formation also of small amounts of a pyridine derivative. In fact, Hinkel and Hey conclude that the fundamental difference between the pyridine condensation of Hantzsch and that of Biginelli would appear to be due to the fact that in the former the first reaction is between ethyl acetoacetate and ammonia, whereas in the Biginelli reaction the first action consists undoubtedly in the formation of the aldehyde diureide. In the opinion of the authors it is not yet established conclusively that the correct explanation of the mechanism of the Biginelli condensation has been given and the authors are now engaged in a study of this problem.

We have now extended the application of Biginelli's condensation by utilizing a common β-keto ester—ethyl acetoacetate—and by varying the constitution or type of aldehyde combination. Both aliphatic and aromatic aldehydes have been used. As a result we have been able to synthesize several new pyrimidine representatives belonging to Biginelli's series of condensation products. In every case which we have examined we have employed hydrochloric acid to catalyze the condensation reaction. The pyridine condensation of the Hantzsch type apparently does not take place under such experimental conditions. The various 2-keto-1,2,3,4-tetrahydropyrimidines which have been prepared are registered in Table I in the Experimental Part of this paper. All of these pyrimidines will be examined to ascertain their physiological behavior.

After six months' experience with the study of this tetrahydropyrimidine class of compounds, the directions of Hinkel and Hey have again been carried out in an effort at a duplication of them, but in every case the results were negative. With purified ethyl acetoacetate, which did not show the slightest acidity to litmus paper, the reaction mixture was poured into 300 ml. of water and allowed to stand for twenty-four hours, when a yield of only 0.77% was obtained. Redistilled ethyl acetoacetate which had stood for two months and showed a slight acidity to litmus paper gave a yield of pyrimidine equal to 2.3%. Again using the acid-free ester and adding (a) four drops of glacial acetic acid and (b) twenty-five drops of glacial acetic acid to the solution, yields of 3.8 and 16.9%, respectively, were obtained. With these same reagents, and using four drops of concentrated hydrochloric acid as catalyst, the yield of pyrimidine was raised to 78.5%. These experiments demonstrate that the three components react in the Biginelli condensation at a very slow rate unless catalyzed by acid. It appears that the reason for Hinkel and Hey ob-

taining the Hantzsch condensation as a side reaction was because the amount of acid impurities was not sufficient to prevent it.

Experimental Part

Application of Biginelli's Condensation. Preparation of 2-Keto-6-methyl-5-carbethoxy-4-phenyl-1,2,3,4-tetrahydropyrimidine. III

In Ethanol.—A careful study of the experimental conditions influencing Biginelli's reaction has led to the following procedure for preparing this pyrimidine in maximum yield. Fifty-three grams of benzaldehyde, 30 g. of urea, 97.5 g. of ethyl acetoacetate, 200 ml. of absolute ethanol and 40 drops of concentrated hydrochloric acid were refluxed for three hours. The reaction mixture was then cooled to 0°, and the pyrimidine filtered and dried at 50°. The yield here was 93.6 g. The filtrate was then refluxed for two hours longer and finally distilled until 155 ml. of alcohol was collected. On cooling the residue we obtained an additional 21.3 grams of the pyrimidine or a total yield of 88.4% of the theoretical. To purify this substance it was divided into two equal portions, and each fraction dissolved in 800 ml. of 95% boiling alcohol. On cooling, the pyrimidine III separated in colorless crystals melting at 202–204°. The yield of purified material was 102 g. The loss on recrystallization may be materially decreased by distilling the solvent to incipient crystallization, since the pyrimidine dissolves in alcohol slowly and an excess of solvent is generally used.

In Glacial Acetic Acid.—Biginelli's condensation can be applied successfully in glacial acetic acid solution. In order to determine whether this solvent or ethanol was more favorable for the condensation, three experiments were conducted as follows. One-tenth mole each of benzaldehyde and urea, 0.15 mole of ethyl acetoacetate, and eight drops of concentrated hydrochloric acid were taken in individual experiments and treated for three hours as follows: (a) refluxed at 85° in 40 ml. of absolute ethanol; (b) heated at 85° in 40 ml. of glacial acetic acid, and (c) refluxed at 112–125° in 40 ml. of glacial acetic acid. The reaction product in each experiment was obtained by pouring the cooled reaction mixture into 400 ml. of water, filtering and drying. The pyrimidine was recrystallized by dissolving in 400 ml. of boiling ethanol and then distilling 250 to 285 ml. of the solvent. The yields of pyrimidine were (a) 70% (m. p. 201.5–203°); (b) 68.1% (m. p. 201–203°); (c) 63.5% light yellow crystals (m. p. 201.5–203°). Thus the tetrahydropyrimidine may be prepared in similar yield and purity in either ethanol or glacial acetic acid at 85°.

Hinkel and Hey's Modification of Biginelli's Condensation Reaction.—The procedure of Hinkel and Hey for the preparation of the tetrahydropyrimidine III in ethanol was repeated but without success after four trials. However, if four drops of concentrated hydrochloric acid for each 0.05 mole of urea were added before refluxing, the Biginelli condensation was accomplished successfully and the tetrahydropyrimidine III was obtained in better yields than those reported by Hinkel and Hey. Their directions for carrying out the condensation with thiourea, ethyl acetoacetate and benzaldehyde to obtain the thiopyrimidine V were also repeated, but without success, unless a few drops of concentrated hydrochloric acid were added as a catalyst. In this connection it is also important to note that Biginelli did not specify the use of hydrochloric acid when he prepared his pyrimidine III, but he did mention its use in the application of the condensation reaction between benzaldehyde and β-carbamidocrotonic ester.

Hinkel and Hey postulated that the Biginelli condensation first involves the formation of an aldehyde-diureide as an intermediate and introduced two equivalents of ethyl acetoacetate, believing that this extra equivalent was necessary to convert the diureide into ethyl β-carbamidocrotonate, thus leading to an improved yield of the pyrimidine III.

TABLE I

2-KETO-6-METHYL-5-CARBETHOXY-4-R-1,2,3,4-TETRAHYDROPYRIMIDINES

R-	Aldehyde RCHO	Moles Urea	Ester	Solvent, ml.	Drops concd. HCl	Reflux time, hrs.	Solvent	Yield, %	M. p. uncorr., °C.	Analyses, % N Calcd.	Found	
Phenyl- (1)	0.5	0.5	0.75	EtOH 200	40	3	EtOH	78.5	202.4	..	..	..
4-Hydroxyphenyl- (2)	.2	.2	.3	EtOH 50	12	3	EtOH	66.5	227–229	10.14	9.97	9.98
4-Methoxyphenyl- (3)	.2	.2	.3	EtOH 80	16	3	EtOH	61.2	201–202	9.65	9.37	9.41
4-Nitrophenyl-	.066	.066	.1	AcOH 100	8	3	EtOH	58.4	207–208.5	13.77	13.57	13.61
4-Nitrophenyl-	.072	.072	.108	EtOH 40	6	4	Aq-EtOH	31.3	207–208.5	..	..	..
3-Nitrophenyl-	.3	.3	.3	EtOH 75	12	6	BuOH	56.6	226–227.5	..	..	..
Styryl- (4)	.5	.5	.75	AcOH 350	0	0	BuOH	71.4	238–239.5	..	..	..
2-Phenylethyl- (5)	.1	.1	.15	AcOH 70	0	0	Aq-EtOH	13.5	179.2–180.2	9.71	9.60	9.53
n-Hexyl- (6)	.5	.5	.75	EtOH 100	40	5.5	Aq-EtOH	7.6	151–152	10.44	10.54	10.55
Hydrogen- (7)	..	..	.45	AcOH 150	20	5	EtOH	17.9	253.8–256	..	..	..
Methyl-	.15	.10	.15	EtOH 20	8	3	Aq-EtOH	25.8	189–190	..	..	..
Methyl- (8)	.15	.10	.15	Dioxane 40	5	2	.....	46.9	181–184	..	..	..
4-Aminophenyl- (9)	..	..	..	.....	..	..	Aq-EtOH	..	220–221	15.27	14.99	14.99
3-Aminophenyl- (9)	..	..	..	.....	..	..	Aq-EtOH	51.6	208.2–209.5	15.27	14.97	14.91
3-Methoxy-4-hydroxyphenyl-	.1	.1	.15	EtOH 40	8	3	EtOH	42.5	232–233	9.15	9.14	8.96
3,4-Dimethoxyphenyl-	.1	.1	.15	EtOH 40	8	2	EtOH	46.9	178–178.5	8.75	8.71	8.70
3,5-Diiodo-4-hydroxyphenyl- (10)	.025	.025	.037	AcOH 30	2	2.25	Gl-AcOH	11.5	216	5.31	5.11	5.10
2,4,6-Trimethoxyphenyl- (11)	.015	.015	.022	EtOH 10	1	2	EtOH	38.1	185–185.5	8.00	7.94	7.99
2-Hydroxyphenyl- (12)	.1	.1	.15	EtOH 40	5	3	EtOH	19.0	201–202	..	..	..
2,4-Dihydroxyphenyl- (13)	.05	.05	.075	AcOH 20	..	..	EtOH	34.2	225.5–226.5	9.59	9.33	9.33
Furyl- (14)	.1	.1	.15	AcOH 40	..	..	EtOH	36.0	204.5–205	..	..	..
3,4-Methylene-dioxyphenyl-	.1	.1	.15	EtOH 40	8	3	EtOH	49.0	187–188	9.21	9.08	9.10
2,6-Dimethyl-1,5-heptadienyl- (15)	.5	.5	.75	AcOH 100	..	5	EtOH	..	150.5–151.5	9.15	904	8.99

COMMENTS ON TABLE I

(1) The actual manipulation of this preparation is described above.

(2) After refluxing the mixture was allowed to stand three days for crystallization.

(3) An additional 3.1 g. of reaction product was obtained by refluxing the filtrate and concentrating the solution.

(4) The components were mixed and allowed to stand for forty-three hours at 25°. During this time 71.4% of the reaction product crystallized out in pure form. The filtrate and washings were allowed to stand for forty-two hours and then poured into water. This gave 12.8 g. more of condensation product, m. p. 236–238°; total yield, 80.3%.

(5) Components allowed to stand for nineteen days at 25° and then poured into 300 ml. of water; the yield was not improved by refluxing in absolute ethanol. *Anal.* Calcd.: C, 66.62; H, 6.99. Found: C, 66.88; H, 6.89.

(6) Was made in two runs of 0.2 mole each and one of 0.1 mole. The reaction mixtures were poured into water and allowed to stand overnight, after which they were combined and the solid separated from oil by filtration. *Anal.* Calcd.: C, 62.64; H, 9.02. Found: C, 62.52; H, 9.16.

(7) 21.3 g. of methylene urea[7] was refluxed with the ketone ester in acetic acid. The suspension of methylene urea gradually dissolved and after filtering, the solution was cooled and poured into 500 ml. of water.

(8) In using dioxane the hydrochloric acid was not added until after one hour of refluxing. When this was added at the beginning, 3.3 g. of alcohol-insoluble material was obtained which melted at 235.5–236.5°. By allowing acetaldehyde and urea to interact in an acidified (hydrochloric acid) water solution at room temperature for several days, a precipitate was obtained which melted at 236.5–237.5°. A mixture of the two products melted at 232–233°.

(9) These two amino derivatives were prepared by hydrogenation of the corresponding nitro compounds with platinum catalyst in glacial acetic acid under three atmospheres of hydrogen. The only loss was that of recrystallization.

The 3-amino compound was also made by reduction of the nitro compound with zinc dust and hydrochloric acid as follows: 15 g. of nitro compound was dissolved in 200 ml. of glacial acetic acid at 75°. After adding 75 g. of zinc dust, 160 ml. of concentrated hydrochloric acid was added in the course of an hour. The solution was then filtered, concentrated *in vacuo* at 75°, cooled, made ammoniacal and filtered. The precipitate was leached twice with concentrated ammonium hydroxide solution, filtered, washed and dried to yield 11.5 g. (85%) of product of m. p. 202.5–206°. After three recrystallizations from aqueous ethanol it melted at 208.5–209.5°. This melting point was not depressed when the material mixed with the 3-amino derivative obtained by catalytic hydrogenation.

(10) The cooled reaction mixture was poured into 350 cc. of cold water. The precipitate was crystallized once from 200 cc. of ethanol and then from glacial acetic acid with the addition of norite.

(11) After filtering the crystals which separated from the cooled reaction mixture, the filtrate was poured into water, a small amount of additional product being thus obtained.

(12) Previously prepared by Biginelli. The cooled reaction mixture was treated with 40 cc. of water and distilled until two phases began to appear. Upon cooling an oil separated which partially crystallized. The product was best purified by dissolving in a minimum of boiling ethanol and distilling to about one-third the volume.

(13) The mixture was allowed to stand at room temperature for four days. The

[7] Dixon and Taylor, *J. Chem. Soc.*, **109**, 1244 (1916).

precipitate was filtered and the filtrate allowed to stand for several weeks, additional material gradually separating. The product was purified by dissolving in a minimum of boiling ethanol and distilling to incipient crystallization.

(14) Previously prepared by Biginelli. The mixture was allowed to stand at room temperature for six days. The precipitate was then filtered and the filtrate poured into water yielding additional product.

(15) The cooled mixture was poured into 1500 cc. of water. An oil separated which partially crystallized upon standing overnight. This was washed with 100 cc. of 65% ethanol in two portions and was then treated with about 500 cc. of petroleum ether. After working well with a spatula, the insoluble material was filtered and washed with petroleum ether. A yield of 40.5 g. or 26.5% of crude product, m. p. 95–110°, was obtained. Fractional crystallization of this material from ethanol yielded in addition to the pyrimidine described in Table I a second product melting at 110–111.5°. *Anal.* Calcd. for $C_{17}H_{26}O_3N_2$ (m. p. 150.5–151.5°): C, 66.63; H, 8.56; N, 9.15. Found: C, 66.91; H, 8.74; N, 9.04, 8.99. Found for compound (m. p. 110–111.5°): C, 66.97; H, 8.69; N, 9.05, 9.05. The apparent isomerism of these two products is being investigated.

In order to determine what amount of β-ketone ester was necessary for producing a maximum yield of pyrimidine III in ethanol in the presence of hydrochloric acid, four experiments were carried out as follows: 0.05 mole each of urea and benzaldehyde were refluxed for two hours in 20 ml. of absolute ethanol with four drops of concentrated hydrochloric acid and with 1.0, 1.25, 1.5 and 2.0 equivalents of ethyl acetoacetate. The yield of the pyrimidine III crystallizing out on cooling was 58.5, 61.5, 67.7 and 64.6%, respectively. Evidently two equivalents of ethyl acetoacetate as used by Hinkel and Hey are excessive and in our condensations reported in this paper where ethyl acetoacetate was employed, 1.5 equivalents of the reagent were used.

As stated above, Hinkel and Hey detected small quantities of a pyridine derivative (4-phenyl-3,5-dicarbethoxy-dihydro-lutidine) by decomposition of the pyrimidine derivative formed in the Biginelli condensation with dilute nitric acid and precipitating the lutidine by addition of alkali. In order to determine whether there was any evidence of a Hantzsch condensation taking place under the experimental conditions used in our work, we performed the following experiment. One-tenth mole each of benzaldehyde, urea, and 0.15 mole of ethyl acetoacetate were refluxed for four hours in 40 ml. of absolute ethanol in the presence of six drops of concentrated hydrochloric acid. The cooled mixture was distinctly acid to litmus paper. It was made alkaline with 10% sodium hydroxide solution and poured into 200 ml. of water. The dried precipitate weighed 21.5 g. This was then decomposed by refluxing for four hours with 300 ml. of dilute nitric acid. The filtered solution was cooled. On making alkaline there was no precipitation of the lutidine derivative. From this result we conclude that the Hantzsch condensation does not take place to any appreciable extent by applying the Biginelli condensation in the presence of hydrochloric acid.

In Table I are recorded data from the preparations of the tetrahydropyrimidines by application of the Biginelli condensation. These substances were desired for pharmacological work, and therefore the condensation mixture was examined solely for these products. Undoubtedly the yields could be improved by variations in experimental technique. Several of these condensations are now being studied more critically in order to obtain a better understanding of the reaction mechanism and also to determine the possibility of isomerization. Details of manipulation in addition to the notes under Table I are not given, for the sake of brevity. The drops of hydrochloric acid were measured from a 5 ml. pipet. Practically all the recrystallizations were carried out by dissolving the pyrimidine in the solvent under a reflux condenser and then distilling to

incipient crystallization. Absolute ethanol and glacial acetic acid were the solvent media used for the condensation reactions.

Summary

1. The authors have reëxamined the condensation reaction described originally by Biginelli, which involves a combination between urea, a β-ketone ester and an aldehyde.

2. We have extended the application of this condensation reaction and find that the change is accelerated by the use of hydrochloric acid.

3. The condensation can be applied in either absolute alcohol or glacial acetic acid solutions.

4. Several new aldehydes have been incorporated in the reaction and several new 2-keto-1,2,3,4-tetrahydropyrimidines have been described.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS AND COMPANY]

OPTICAL PROPERTIES OF SOME DERIVATIVES OF LOWER ALIPHATIC ALCOHOLS AND ALDEHYDES

BY W. M. D. BRYANT

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Among physical methods of identifying closely related organic compounds, those of optical crystallography offer great promise both from the standpoint of speed and sensitivity.[1] The members of homologous series of organic compounds, because of their gradual changes in chemical and ordinary physical properties with increasing molecular weight, place great obstacles in the way of the chemist attempting their identification. A number of optical crystallographic properties can be observed by means of the polarizing microscope, many of which are, for all practical purposes, independent physical constants, and greatly increase the possibility of a precise identification of closely related compounds.

The scheme of optical identification employed in this research is one successfully used by Wright,[1] Wherry,[2] Keenan[3] and others,[4] and depends upon the determination of such properties as refractive index, optic axial angle, extinction angle, optical character, dispersion, together with the orientation of the optical ellipsoid within the crystal. This characteriza-

[1] Wright, THIS JOURNAL, **38**, 1647 (1916).

[2] Wherry, *U. S. Dept. Agr. Bull.*, No. 679 (1918); Wherry and Yanovsky, THIS JOURNAL, **40**, 1063 (1918).

[3] Keenan, *J. Biol. Chem.*, **62**, 163 (1924); Keenan and Weisberg, *J. Phys. Chem.*, **33**, 791 (1929); Phillips and Keenan, THIS JOURNAL, **53**, 1924 (1931).

[4] Poe and Sellers, *ibid.*, **54**, 249 (1932); Kofler and Mayrhofer, *Mikrochemie*, **10**, 460 (1932); Takahashi and Yaginuma, *J. Soc. Chem. Ind. Japan, Suppl.*, **33**, 370 (1930).