[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Reaction of Guanidine with α,β-Unsaturated Carbonyl Compounds. I. Cinnamic Acid Derivatives

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RECEIVED JULY 30, 1953

The reaction between guanidine base and certain cinnamic acid derivatives has been examined. Methyl cinnamate gave only modest yields of the expected dihydropyrimidine along with some cinnamoylguanidine.

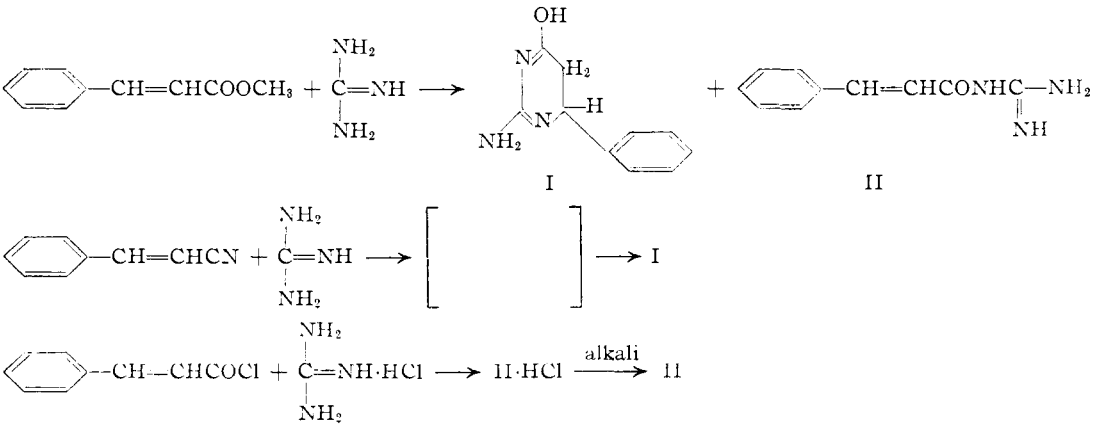
Among the numerous synthetic routes to substituted pyrimidines the reaction of α-formyl or α-acyl acetic esters with various urea derivatives, such as guanidine, thiourea and amidines, is well known and has been much used. Less has been done with attempts to combine these urea derivatives with α,β-unsaturated carbonyl compounds. Traube and Schwarz[1] found that mesityl oxide condensed readily with guanidine and benzamidine to give crystalline dihydropyrimidine derivatives. They also reported that several other α,β-unsaturated carbonyl compounds reacted easily with guanidine and benzamidine, but either no crystalline products were isolated, or the reaction products were more complex in nature. Additional successful pyrimidine condensations of this type have been presented more recently by Dodson and Seyler.[2] Fischer and Roeder[3] obtained 4-phenyldihydrouracil by heating cinnamic acid with urea. Traube[1] mentioned in a footnote that one of his students, E. Köhler, had isolated a white crystalline solid from the reaction of ethyl cinnamate and guanidine, and this was considered to be the dihydropyrimidine I (see Chart I) although no yield, melting point or analytical data were supplied.

Methyl cinnamate was refluxed for 20 hours with slightly more than one molecular equivalent of guanidine base in ordinary absolute alcohol solution. The products isolated were 2-amino-4-hydroxy-6-phenyl-5,6-dihydropyrimidine (I) (see Chart I), 25–30% yield, cinnamoylguanidine (II) (see Chart I), 5–10% yield, cinnamic acid, 25–30%, and unreacted cinnamic ester, 10–15%. Cinnamic acid resulted presumably from strong basic hydrolysis of some of the cinnamic acid derivatives by means of small amounts of water present in the commercial absolute alcohol. When the condensation procedure was repeated using as a solvent methanol, especially dried over magnesium just before use, the yields and nature of the products isolated were not altered significantly except that more methyl cinnamate and no cinnamic acid was recovered.

Under similar reaction conditions cinnamonitrile and guanidine gave a 10–20% yield of I as the only

CHART I

REACTION OF GUANIDINE WITH SOME CINNAMIC ACID DERIVATIVES



It thus seemed to be of interest to examine the behavior of guanidine with various α,β-unsaturated acid derivatives because this might lead to the synthesis of useful pyrimidine compounds and at the same time might afford a comparison of the reactivities of the α,β-double bond and the carbonyl double bond toward this reagent. The particular substances used in this work were methyl cinnamate, cinnamonitrile and cinnamoyl chloride. These cinnamic acid derivatives were selected for the initial work for ease of handling and the relative simplicity of the products to be expected to result from them.

(1) W. Traube and R. Schwarz, *Ber.*, **32**, 3163 (1899).
(2) R. M. Dodson and J. K. Seyler, *J. Org. Chem.*, **16**, 461 (1950).
(3) E. Fischer and G. Roeder, *Ber.*, **34**, 3751 (1901).

product isolated, instead of the expected diamino analog. The reaction mixture in this case smelled strongly of both ammonia and cinnamonitrile. It is not known whether the diaminopyrimidine or some open chain analog is the intermediate from which ammonia is easily displaced to yield I.

The identity of samples of I, obtained from methyl cinnamate and from cinnamonitrile, was established by melting points, analyses for carbon, hydrogen and nitrogen and by comparison of their ultraviolet absorption spectra.

The structure of the cinnamoylguanidine (II) was established by preparing it independently by heating cinnamoyl chloride with guanidine hydrochloride. In this reaction the hydrochloride of II is the immediate product and since no free guanidine base was involved it was felt that only the more reactive acid chloride function could be attacked. Liberation of the free base gave the same product as one of the fractions obtained from the interaction of guanidine with methyl cinnamate. Melting points, analyses and absorption spectra of the samples of II from the two routes were the same. This was also true for the hydrochlorides, II·HCl. Furthermore, the ultraviolet spectra for both II and II·HCl were quite similar and resembled the spectra of cinnamic acid and its amide while differing significantly from that of I. Cinnamic acid and its amide (λ_{max} 273 mμ, ϵ 21,100, and λ_{max} 272 mμ, ϵ 20,200, respectively) have intense absorption at 273 mμ while for II and II·HCl the wave length for λ_{max} is increased to 290 and 296 mμ with a simultaneous increase in ϵ to 26,000–27,000. This bathochromic shift may be associated with the electronic interaction possible between the styryl and guanidine groups across the carbonyl. The λ_{max} for I has been shifted far to the left, to 238.5 mμ with a marked decrease in intensity, to 13,000 probably to be associated with the lack of electronic interaction between the benzene and guanidine systems. The hydrochloride of I, I·HCl, has no appreciable absorption above 220 mμ.

It appears likely that II is not an intermediate in the formation of I. In the 90-hour run the yields of both I and II increased in parallel fashion. In addition a series of experiments was performed attempting to convert II to I but with no success. When II, as the base, was heated for long periods in benzene, methanol, water, methanol with a trace of sodium methylate, or methanol with one equivalent of sodium methylate no I could be isolated from the products. Usually II was recovered unchanged, or was converted to a more or less extent into methyl cinnamate or cinnamic acid, depending on the particular reaction conditions.

These results suggest that methyl cinnamate reacts with guanidine by two simultaneous paths as first steps, addition to the α,β-double bond and amide formation with the ester to give II. Since II is not readily convertible to I, I presumably must result from the β-guanidino ester formed by addition across the C–C double bond.

In the somewhat related compound methyl acrylate it is well known that amines react much more rapidly by addition across the α,β-double bond than they do in amide formation. It is therefore by no means unreasonable that the substitution of the β-phenyl group onto methyl acrylate could slow down the preferred addition reaction to result in more nearly equal rates for the two processes.

Experimental

Reaction of Methyl Cinnamate with Guanidine. (A).—A solution containing 8 g. (0.05 mole) of methyl cinnamate and 3.6 g. (0.06 mole) of free guanidine in 100 cc. of commercial absolute ethyl alcohol was refluxed for 20 hours on a steam-bath. After evaporation to 15–20 cc. volume a white product separated on cooling. This subsequently was shown to be 2-amino-4-hydroxy-6-phenyl-5,6-dihydropyrimidine, compound I. After several recrystallizations from methanol the yield of pure white crystals was 2.5–3.0 g. (25–30%), m.p. 266–267°.

Anal. Calcd. for $C_{10}H_{11}ON_3$: C, 63.5; H, 5.9. Found: C, 63.4; H, 5.8.

The hydrochloride of I was precipitated from a solution of I in methanolic hydrogen chloride with ether. It was purified by recrystallization from methanol–ether mixtures and then melted at 214–215°.

Anal. Calcd. for $C_{10}H_{12}ON_3Cl$: C, 53.3; H, 5.4. Found: C, 53.4; H, 5.4.

(B).—The ethanol mother liquors from the original reaction mixture, after filtration of I, were evaporated to dryness and gave 8 g. of a pasty solid. This was treated with methanolic hydrogen chloride (about 30%) to pH < 1, and the small amount of white insoluble crystals was removed by filtration. After recrystallization from methanol there was obtained 1 g. (10%) of white crystals melting at 269–270°.

Anal. Calcd. for $C_{10}H_{12}ON_3Cl$: C, 53.3; H, 5.4. Found: C, 53.1; H, 5.6.

This substance was later shown to be cinnamoylguanidine hydrochloride, II·HCl. When this hydrochloride was suspended in hot water and treated with an excess of concentrated sodium hydroxide solution (20%) the base cinnamoylguanidine precipitated. It was recrystallized from water (the solution had a pH of 8–9) and then melted at 140–141°.

Anal. Calcd. for $C_{10}H_{11}ON_3$: C, 63.5; H, 5.9. Found: C, 63.3; H, 5.6.

After drying *in vacuo* or recrystallization from absolute ethanol–benzene mixtures the base melted at 152–153°. This suggests that the product crystallized from water may be a hydrate which loses water during the drying which precedes analysis (2 hr. at 100° *in vacuo*).

(C).—The methanolic hydrogen chloride filtrates from II·HCl were evaporated to dryness. The residue was extracted with ether, and after evaporation 3.5 g. of ether soluble and about 3 g. of ether insoluble material remained. The ether soluble fraction made alkaline with dilute sodium hydroxide and again extracted with ether gave about 1 g. of cinnamic ester in the ether soluble layer and 2.5 g. of cinnamic acid, m.p. 132–133°, was precipitated from the aqueous alkali with hydrochloric acid.

The less than 3 g. of ether-insoluble material was presumed to be mainly guanidine hydrochloride and gave no further isolable amounts of the products described above.

The cinnamic acid isolated in this experiment was believed to be derived from hydrolysis of methyl cinnamate by the small amounts of water present in the commercial absolute ethanol. Since the reaction medium was at pH > 11 from the free guanidine the conditions would be favorable for strong basic hydrolysis.

When the above condensation experiment was repeated using as a solvent methanol, freshly dried over magnesium, the results differed principally in the recovery of more methyl cinnamate and no cinnamic acid.

Condensation of Cinnamonitrile with Guanidine.—A solution containing 6.5 g. (0.05 mole) of cinnamonitrile and 3.6 g. (0.06 mole) of guanidine base in 100 cc. of commercial absolute ethyl alcohol was refluxed for eight hours on a steam-bath. The solution was concentrated to 15 cc. and excess ether was added precipitating 10–12 g. of a viscous, oily mass, insoluble in ether. The ether-insoluble oil crystallized in part from methanol to give 1 g. (10–15%) of solid product. This was recrystallized several times from methanol and gave 0.8 g. of white crystals, m.p. 265–267°.

Anal. Calcd. for $C_{10}H_{11}ON_3$: C, 63.5; H, 5.9; N, 22.2. Found: C, 63.4; H, 5.5; N, 22.5.

The original reaction mixture smelled strongly of ammonia and of cinnamonitrile. No more solid product was readily obtainable from the mother liquors either from the basic solution or after acidifying with methanolic hydrogen chloride. These mother liquors were not investigated further.

Reaction of Cinnamoyl Chloride and Guanidine.—Several different sets of conditions were explored in trying to obtain cinnamoylguanidine from cinnamoyl chloride. The cinnamoyl chloride was treated with guanidine as the hydrochloride salt, as the carbonate, as the free base in water, in acetone and in benzene.

Cinnamoylguanidine hydrochloride, II·HCl, was ob-

tained best by heating cautiously over a free flame a mixture of cinnamoyl chloride with two equivalents of guanidine hydrochloride until an exothermic reaction was initiated with copious evolution of hydrogen chloride. When the violent process had subsided the reaction mixture was stirred up with acetone, which was filtered and discarded. The insoluble solid was recrystallized from methanol to give a 70–80% yield of cinnamoylguanidine hydrochloride, m.p. 269–270°. Cinnamoylguanidine base liberated from this hydrochloride and recrystallized from water melted at 141–142°.

Using guanidine carbonate instead of the hydrochloride a small yield of II·HCl was obtained by a similar procedure.

Cinnamoyl chloride with excess aqueous guanidine base gave almost entirely cinnamic acid.

Excess guanidine base reacted with cinnamoyl chloride in dry benzene to give as the chief product isolated, although in moderate yield, dicinnamoylguanidine hydrochloride. This was recrystallized from methanol to give white crystals, m.p. 225–226°.

Anal. Calcd. for $C_{19}H_{18}O_2N_3Cl$: C, 64.1; H, 5.1. Found: C, 64.4; H, 5.1.

Attempts to Cyclize Cinnamoylguanidine (II) to the Dihydropyrimidine (I).—Numerous attempts were made to cyclize the open chain cinnamoylguanidine base (II) using conditions some of which resembled those prevailing in the condensation of methyl cinnamate with guanidine. In no case was any isolable amount of I obtained. In most cases the starting compound II, methyl cinnamate, and cinnamic acid were the only substances recovered. These facts seem to indicate that II is not an intermediate in the formation of I.

Ultraviolet Absorption Spectra.—The ultraviolet spectra were obtained using a Beckman quartz spectrophotometer model DU, cell length 1 cm., and solutions were made up at a concentration of 10 mg. per liter in 95% ethyl alcohol.

Acknowledgment.—The authors are indebted to S. W. Blackman and N. Martinez, Jr., for the microanalytical results included and to Miss Dian Cameron for the ultraviolet absorption spectra.

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2-Vinylpyrrole and Homologs

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RECEIVED AUGUST 13, 1953

2-Pyrrolecarbinols are obtained in excellent yield by the inverse lithium aluminum hydride reduction of 2-pyrrole ketones. Their dehydration furnishes fair yields of homologs of 2-vinylpyrrole. 2-Vinylpyrrole itself is best prepared by vapor phase dehydration of 2-pyrroleethanol.

The recent literature contains a number of references to the preparation of five-membered heterocyclic analogs of styrene which have been carried out primarily to study the polymerizability of such substances. Thus 2-vinylfuran,[2] 2-vinylthiophene,[3] 2-vinylthiazole[4] and 2-vinylimidazole[5] are known and several homologs have been synthesized.[6] On the other hand, the properties of 2-vinylpyrrole are not recorded although there exists a patent[7] which claims that it may be made by dehydrogenation of 2-ethylpyrrole.

A priori, one might expect considerable instability in a compound of this type, in spite of the fact that polysubstituted vinylpyrroles, which are of interest because of their close relationship to naturally-occurring pigments, exhibit no tendency to decompose or to polymerize. In view of our interest in the chemistry of simple monofunctional derivatives of pyrrole we have undertaken the investigation of 2-vinylpyrrole and its homologs. The present paper describes the synthesis of 2-vinyl-, 2-propenyl- and 2-(β-styryl)-pyrrole by methods which are capable of extension to other compounds.

(1) Abstracted from the thesis of Charles F. Courtney submitted in partial fulfillment of the requirements for the degree Master of Science, 1953.

(2) M. Moureu, C. Dufraisse and J. R. Johnson, *Ann. chim.*, [10] **7**, 15 (1927).

(3) R. Kuhn and O. Dann, *Ann.* **547**, 293 (1941); D. T. Mowry, M. Renoll and W. F. Huber, THIS JOURNAL, **68**, 1105 (1946); R. T. Nazzaro and J. L. Bullock, *ibid.*, **68**, 2121 (1946).

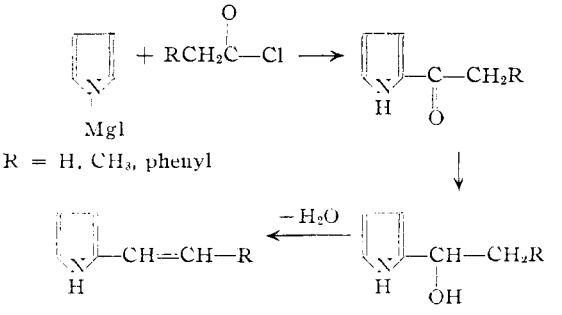
(4) D. L. Schoene, *ibid.*, **73**, 1970 (1951).

(5) J. K. Lawson, Jr., *ibid.*, **75**, 3398 (1953).

(6) For examples, see G. B. Bachman and L. V. Heisey, *ibid.*, **70**, 2378 (1948); **71**, 1985 (1949); R. H. Wiley and N. R. Smith, *ibid.*, **72**, 5198 (1950).

(7) C. R. Wagner, U. S. Patent No. 2,393,132 (Jan. 15, 1946).

The scheme for the preparation of the desired substances is



The reduction of pyrrolealkyl ketones to pyrrolealkylcarbinols has so far not been accomplished satisfactorily. Dennstedt and Zimmermann[8] reduced 2-acetylpyrrole with sodium amalgam and reported the isolation of two products in unstated yield, one a solid, presumably a pinacol, the other a high-boiling liquid, probably the expected carbinol. Hess and co-workers[9] demonstrated that the pyrrole ring as well as the carbonyl group of 2-acylpyrroles was reduced by means of sodium and ethanol or by catalytic hydrogenation at low pressure. High pressure hydrogenation, on the other hand, apparently cannot be stopped at the carbinol stage, but proceeds further, through hydrogenolysis, to give an alkylpyrrole.[10]

(8) M. Dennstedt and J. Zimmermann, *Ber.*, **19**, 2204 (1886).

(9) K. Hess, *ibid.*, **46**, 3113 (1913); K. Hess, F. Merck and C. Uibrig, *ibid.*, **48**, 1886 (1915).

(10) M. DeJong and J. P. Wibaut, *Rec. trav. chim.*, **49**, 237 (1930); F. K. Signaigo and H. Adkins, THIS JOURNAL, **58**, 709 (1936); J. L. Rainey and H. Adkins, *ibid.*, **61**, 1104 (1939); H. Adkins and H. L. Coonradt, *ibid.*, **63**, 1563 (1941).