to stand at room temperature for two days. Evaporation of the methylamine left a white solid; weight, 185 mg. (73% yield). After crystallization from acetonitrile the methylamide formed colorless crystals which melted with decomposition at 235–240° (in a capillary tube); on the Dennis–Shelton bar the substance decomposed instantly at 258°.

Anal. Calcd. for $C_{12}H_{14}O_3N_2$: N, 11.2. Found (micro-Dumas): N, 11.24.

Reaction with Alkali.—(a) A mixture of 433 mg. of the methylamide and 30 ml. of 20% aqueous potassium hydroxide solution was refluxed for one and one-half hours. The methylamine formed was swept out of the system by a current of nitrogen and absorbed in 20 ml. of 0.1 *N* hydrochloric acid. The alkaline hydrolysate was cooled and acidified by the addition of 9 ml. of concentrated hydrochloric acid. The precipitated acid was collected and washed with water. Without further purification the product melted at 203–204.5°, and was identified as indole-2-carboxylic acid by comparison with an authentic sample. The accessory product of hydrolysis, methylamine, was identified as the hydrochloride, m. p. 222–225°.

(b) A 200-mg. sample of the methylamide (V) was dissolved by gentle warming in 15 ml. of *N*/3 methanolic potassium hydroxide solution. After four hours of standing at 25°, carbon dioxide was bubbled into the solution to convert excess alkali to the carbonate. The reaction mixture was evaporated to dryness under diminished pressure and the solid residue was taken up in water. All but a small portion of the solids dissolved in water; the identity of the insoluble material, m. p. 165–175°, was not established. The filtered aqueous solution was acidified with hydrochloric acid and cooled at −5° for several hours. The colorless crystalline solid which separated was collected and identified as the methylamide of indole-2-carboxylic acid, m. p. 219–220°. The yield was 65% of the theoretical.

Reaction with Acid.—A 50-mg. sample of the methylamide (V) was dissolved in 0.5 ml. of 50% aqueous sulfuric acid. After standing for one-half hour at room temperature colorless crystals began to separate. After two hours of standing 1 ml. of water was added and the crystals were collected and washed with water; weight, 16 mg. Recrystallization from 95% ethanol gave colorless crystals, m. p. 220–221°, which were identified as the methylamide of indole-2-carboxylic acid by comparison with an authentic sample.

Summary

The methyl ester and methylamide of 1-acetyl-3-hydroxyindoline-2-carboxylic acid have been synthesized as model compounds of the hydroxyindoline system that has been postulated to occur in gliotoxin and desthiogliotoxin. The anticipated transformation of the model compounds into derivatives of indole-2-carboxylic acid by the action of acids and of alkalies was confirmed experimentally. The behavior of the model compounds is therefore compatible with the view that the various derivatives of indole-2-carboxylic acid formed from gliotoxin and desthiogliotoxin arise from the presence of a 3-hydroxyindoline grouping.

ITHACA, NEW YORK RECEIVED SEPTEMBER 15, 1949

[CONTRIBUTION NO. 742 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

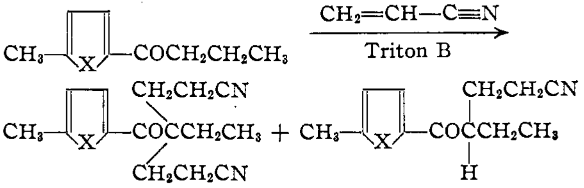
The Cyanoethylation of Certain Alkylated Heterocyclic Ketones[1]

BY NANCY A. ACARA AND ROBERT LEVINE

The cyanoethylation of a number of different types of active hydrogen compounds has been studied by Bruson and co-workers.[2] Among the compounds which were cyanoethylated are alkyl, alkylaryl and alkylheterocyclic ketones. In this laboratory, we have recently extended this work to the cyanoethylation of a number of β-keto-esters and β-diketones.[3]

The present study on the cyanoethylation of several alkylated ketones in the thiophene and furan series was undertaken in order to determine what effect an alkyl group present in the heterocyclic ring would have on the nature of the condensation products formed. Thus, 5-methyl-2-(acetyl, propionyl and *n*-butyryl)-furan, 5-methyl-2-(acetyl, propionyl and *n*-butyryl)-thiophene and 2,5-dimethyl-3-(acetyl, propionyl and *n*-butyryl)-furan were treated with acrylonitrile in the presence of the basic condensing agent, "Triton B."

The yields and physical constants of the condensation products are found in Table I. It may be seen that 5-methyl-2-acetyl-(furan and thiophene) have been tricyanoethylated and the corresponding ethyl ketones dicyanoethylated in good yields. However, the homologous *n*-propyl ketones gave a mixture of mono- and dicyanoethylated derivatives as indicated by the following equation in which X represents an oxygen or sulfur atom.



In order to determine whether a heterocyclic *n*-propyl ketone of the furan or thiophene series which does not contain an alkyl group in the ring would also give rise to a mixture of condensation products, 2-*n*-butyrylthiophene was cyanoethylated and a mixture of the mono (36%) and the dicyanoethylated (48.5%) ketones was isolated. This result is unexpected because the cyanoethylation of 2-*n*-butyrylfuran has apparently

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[1] This paper is based on a thesis submitted by Nancy A. Acara in partial fulfillment of the requirements for the degree of Master of Science at the University of Pittsburgh.

[2] See Bruson, "Organic Reactions," Vol. 5, Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1949, Chapter 2.

[3] Zellars and Levine, *J. Org. Chem.*, **13**, 911 (1948).

TABLE I

CYANOETHYLATED KETONES

Ketone	Cyanoethylation products	B. p. or m. p. °C.	Mm.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-*n*-Butyrylthiophene	Mono	154-156	2.5	36[e]	$C_{11}H_{13}OSN$					6.76	6.43
	Di	M 95.5-96[a,b]		48.3[e]	$C_{14}H_{16}OSN_2$[j]					10.77	11.02
5-Methyl-2-acetylfuran	Tri	M 177-177.7[a,c]		70.9[e]	$C_{16}H_{17}O_2N_3$	67.82	67.69	6.04	6.28	14.86	14.81
5-Methyl-2-propionylfuran	Di	215-218	3								
		M 58-59[a,c]		61.5[e]	$C_{14}H_{16}O_2N_2$	68.86	69.16	6.58	6.57	11.47	11.50
5-Methyl-2-*n*-butyrylfuran	Mono	153-154.5	5	22.9[f]	$C_{12}H_{15}O_2N$	70.22	69.99	7.37	7.08	6.83	7.14
	Di	M 93-94[a,c]		47.2[f]	$C_{15}H_{18}O_2N_2$	69.74	69.96	7.02	6.75	10.85	10.94
5-Methyl-2-acetylthiophene	Tri	M 130.5-131.5[a,c]		79.6[e]	$C_{16}H_{17}OSN_3$[k]	64.21	64.19	5.69	5.55	14.05	13.82
5-Methyl-2-propionylthiophene	Di	M 79-80[a,c]		70.4[e]	$C_{14}H_{16}OSN_2$[l]	64.62	64.66	6.15	6.39	10.77	10.95
5-Methyl-2-*n*-butyrylthiophene	Mono	159-160	2	42.7[e]	$C_{12}H_{15}OSN$[m]					6.43	6.35
	Di	M 87-88[a,b]		27.2[e]	$C_{15}H_{18}OSN_2$[n]					10.22	10.04
2,5-Dimethyl-3-acetylfuran	Tri	M 169.5-170[a,c]		15.7[g,h]	$C_{17}H_{19}O_2N_3$					14.14	13.89
2,5-Dimethyl-3-propionylfuran	Mono	157-157.5	8	27.3[e]	$C_{12}H_{15}O_2N$	70.22	70.24	7.38	7.24	6.83	7.11
	Di	217-221	3								
		M 86-87[a,c]		45.3[e]	$C_{15}H_{18}O_2N_2$	69.74	69.86	7.02	6.75	10.85	10.84
2,5-Dimethyl-3-*n*-butyrylfuran	Mono	137.5-138	2	54.3[g,i]	$C_{13}H_{17}O_2N$					6.39	6.52
		M 51-52[a,d]									

[a] M stands for m. p. [b] Recrystallized from a petroleum ether–benzene mixture. [c] Recrystallized from 95% ethanol. [d] Recrystallized from petroleum ether (30–60°). [e] Reaction time two hours after addition of acrylonitrile. [f] Reaction time five days after addition of acrylonitrile; in two hours none of the mono and 22.3% of the di compound was obtained; in one day 26.1% of the mono and 40.3% of the di compound was obtained. [g] Reaction time seven days after addition of acrylonitrile. [h] In 2 hours only an 11.3% of the tri compound was obtained. [i] In 2 hours no mono compound was obtained. [j] Calcd.: S, 12.31. Found: S, 12.43. [k] Calcd.: S, 10.70. Found: S, 10.58. [l] Calcd.: S, 12.31. Found: S, 12.56. [m] Calcd.: S, 14.48. Found: S, 14.31. [n] Calcd.: S, 11.68. Found: S, 11.63.

resulted in the formation of only a dicyanoethylated derivative.[4]

It may be seen (Table I) that the cyanoethylation of the 2,5-dimethyl-3-acylfurans, in which the acyl and methyl groups occupy adjacent positions in the furan ring, has given some interesting results. Thus, the methyl ketone has been tricyanoethylated in low yield regardless of whether the reaction time was two hours (11.3%) or seven days (15.7%). The ethyl ketone gave a mixture of mono- (27.3%) and dicyanoethylated (45.3%) products and the *n*-propyl ketone gave a 54.3% yield of the monocyanoethylated derivative when the reaction time was seven days. It is quite possible that these results are due to steric interference between the methyl group in the two position and the acyl groups in the three position of the 2,5-dimethyl-3-acylfurans.

Finally, 2,5-dimethyl-3-propionylfuran and 5-methyl-2-*n*-butyrylthiophene have been cyanoethylated so that the only product formed in each case was the monocyanoethylated derivative. This has been accomplished in 43.2% yield with the former and in 56% yield with the latter ketone by allowing a methanolic solution of one equivalent of acrylonitrile and two equivalents of ketone to react in the presence of one equivalent of sodium methoxide for three hours at the boiling point of the mixture.

Experimental

The ketones used in this study were prepared by the boron fluoride etherate method[5,6] recently developed in this laboratory and were washed with sodium bicarbonate solution and redistilled before use.

General Procedure for the Cyanoethylation of Ketones in the Presence of Triton B.—In a 500-ml. round-bottom three-neck flask equipped with a mercury-sealed stirrer, a dropping funnel and a thermometer were placed 0.2 mole of the ketone, 25 g. of *t*-butyl alcohol and 3 g. of Triton B (benzyltrimethylammonium hydroxide). To the rapidly stirred mixture, the acrylonitrile (0.6 mole in the case of a methyl ketone and 0.4 mole in the case of an ethyl or *n*-propyl ketone) was added over a 30–45 minute period, keeping the reaction temperature at 25–30° by occasionally immersing the flask in an ice-bath. After stirring the reaction mixture for the length of time indicated in the footnotes to Table I (more *t*-butyl alcohol being added if the mixture gets too thick to stir), the contents of the flask was poured onto crushed ice and acidified with concentrated hydrochloric acid. If a solid precipitated it was filtered, recrystallized and analyzed. The filtrate (or the acidified reaction mixture if no solid precipitated) was extracted with several portions of ether. The combined ether extracts were dried over Drierite, the solvent distilled at atmospheric pressure and the residue fractionated in vacuum to give the cyanoethylated ketones, samples of which were analyzed.

Monocyanoethylation of Ketones in the Presence of Sodium Methoxide.—The apparatus used is the same as that described above except that the thermometer is replaced by a reflux condenser carrying a drying tube filled with Drierite. Two-tenths of a mole of the ketone, 0.1 mole of sodium methoxide and 150 ml. of absolute methanol are placed in the flask. The rapidly stirred mixture is brought to reflux by means of a water-bath and to this refluxing solution, 0.1 mole of acrylonitrile is added over a period of fifteen minutes. The mixture is refluxed for three hours longer and then the methanol is removed by distillation at atmospheric pressure. The residue is poured onto ice acidified with concentrated hydrochloric acid and worked up as described above.

Using this procedure, 2,5-dimethyl-3-propionylfuran has been monocyanoethylated to give γ-(2,5-dimethyl-3-furoyl)-valeronitrile b. p. 157–158° at 8 mm. in 56% yield and 5-methyl-2-*n*-butyrylthiophene has given γ-(5-methyl-2-thenoyl)-capronitrile, b. p. 159–160° at 2 mm. in 43.2% yield.

Summary

A number of alkylated thiophene and furan

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(4) Bruson and Riener, THIS JOURNAL, **70**, 214 (1948).

(5) Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).

(6) Levine, Heid and Farrar, THIS JOURNAL, **71**, 1207 (1949).

ketones has been condensed with acrylonitrile to give cyanoethylated products. In several cases, mixtures of mono- and dicyanoethylated compounds were produced.

Conditions have been found whereby 5-methyl-2-*n*-butyrylthiophene and 2,5-dimethyl-3-propionylfuran may be condensed with acrylonitrile to give only a monocyanoethylated condensation product.

Pittsburgh 13, Pa. Received November 21, 1949

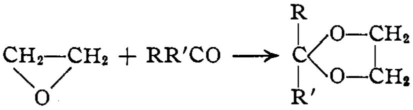
[Contribution from the Department of Chemistry, West Virginia University]

Reactions of Ethyleneimine with Aldehydes and Ketones[1]

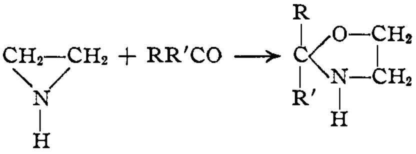
By J. B. Doughty,[2] C. L. Lazzell and A. R. Collett

The structure of ethyleneimine, $\overline{H_2C—CH_2—NH}$, and of ethylene oxide, $\overline{H_2C—CH_2—O}$, suggests that they should react similarly. The reactions of ethylene oxide have been more extensively investigated than those of the imine but where comparable data exist their reactions have been shown to be similar. In order to furnish additional data, a series of reactions of the imine with several aldehydes and ketones has been carried out.

Ethylene oxide reacts with aldehydes and ketones to give cyclic acetals[3,4]



Assuming a parallel reaction for ethyleneimine, oxazolidines would be formed.



The possibility of this reaction appeared even more favorable since oxazolidines have been prepared by the reaction of ethanolamines with aldehydes and ketones to give these cyclic compounds.[5–12] These latter reactions appear to proceed by the formation of an intermediate condensation product which loses water to form the five membered cyclic oxazolidine. Since ethyleneimine is prepared by removing water from monoethanolamine it was thought that the imine might add to aldehydes and ketones to give the heterocyclic compounds.

Experimental

Reagents.—The ethyleneimine used in all reactions was prepared by a modification of the procedure of Wenker[13] which was similar to that proposed by Leighton, Perkins and Renquist.[14] The monoethanolamine used was obtained from Carbide and Carbon Chemicals Corporation. All aldehydes and ketones used were obtained from the Eastman Kodak Company and were treated with appropriate reagents before purification by distillation.

General Procedure.—One mole of aldehyde or ketone was mixed with 100 ml. of either ethyl or isopropyl ether in a 500-ml. round-bottomed flask. This solution was cooled to 5–10° in an ice-water-bath. To the cooled solution a mole of ethyleneimine was added dropwise with one and one-half to two hours being required for the addition. When all the ethyleneimine had been added the flask was fitted with a water cooled condenser and placed over a heating unit. The reaction mixture was refluxed for twenty-four hours or longer and then the ether solvent removed by distillation. The liquid oxazolidines were recovered and purified by vacuum distillation.

Oxazolidines.—Six aldehydes and two ketones were treated with ethyleneimine to give oxazolidines. The yields, analyses and some characteristic constants of these oxazolidines are given in Table I.

The oxazolidines of the lower members of the aliphatic series are water-clear liquids having a characteristic amine-like odor. 2-Phenyloxazolidine is a light yellow liquid. 2-Hexyloxazolidine is a white crystalline solid which is completely soluble in isopropyl ether at room temperature. All products hydrolyze easily in water and decompose when distilled at atmospheric pressure.

Since these oxazolidines hydrolyze easily, this procedure was used to check the composition of the products. Ten grams of each product was mixed with 50 ml. of water and kept at room temperature for two days. After standing the mixtures were made acidic with hydrochloric acid. The two layers formed were separated and the water layer extracted with ethyl ether. The insoluble water layer and the ether extracts were combined. The combined liquids were distilled and the aldehyde or ketone recovered. The water layer was evaporated to dryness and the monoethanolamine hydrochloride crystals obtained were washed with alcohol and ether, then dried and weighed. The results are summarized in Table II.

It will be noted by inspection of Table I that the agreement between the experimental and the calculated values of the molar refraction is good. This favors the presence of the ring structure since an open chain compound would possess unsaturation and therefore a higher value for the molar refraction. Again it will be noted from Table II that when these compounds were subjected to gentle hydrolysis the expected products were identified and

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(1) This paper represents a part of the dissertation submitted by J. B. Doughty in partial fulfillment of the requirements for the Ph.D. degree to the Graduate Faculty of West Virginia University.

(2) Development Department, West Virginia Pulp and Paper Company, Charleston, S. C.

(3) Lawrence, Masters Thesis, West Virginia University, 1942.

(4) Watson, Ph.D. dissertation, West Virginia University, 1936.

(5) L. Knorr and H. Matthes, *Ber.*, **34**, 3485 (1901).

(6) Bergmon, Ulpts and Carnacho, *ibid.*, **55**, 2796 (1922).

(7) M. Meltsner, E. Waldman and C. B. Kremer, This Journal, **62**, 3494 (1940).

(8) E. M. Hancock and A. C. Cope, *ibid.*, **64**, 1503-1506 (1942).

(9) E. M. Hancock and A. C. Cope, *ibid.*, **66**, 1453-1456 (1944).

(10) E. M. Hancock and A. C. Cope, *ibid.*, **66**, 1738-1747 (1944).

(11) Senkus, *ibid.*, **67**, 1515-1519 (1945).

(12) N. K. Ushenko, *C. A.*, **37**, 4395 (1943).

(13) Wenker, This Journal, **57**, 2328 (1935).

(14) Leighton, Perkins and Renquist, *ibid.*, **69**, 1540 (1947).