used with 3,4,5-trimethoxyphenyl substituted oximes. The amines were also prepared directly from the hydrochalcones by the Leuckart reaction.[27] In all cases reported here (except compound 24, Table II) the free bases could not be obtained crystalline. The hydrochlorides were obtained crystalline as colorless needles when a dried solution of the amine in ether was treated with dry hydrogen chloride. Crystallization from absolute alcohol afforded the pure amine salt. The picrates were prepared by treating a solution of the amine in alcohol with excess picric acid. The yellow crystalline picrates were crystallized from alcohol. When the picrate of amine 15 (Table II) was crystallized from absolute alcohol the m.p. was 166–167°. The same picrate crystallized from 50% ethanol melted at 127–129°.

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EDMONTON, ALBERTA, CANADA

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[27] A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp and G. Hennings, THIS JOURNAL, **58**, 1808 (1936).

[CONTRIBUTION FROM THE RICHARDSON CHEMISTRY LABORATORY, TULANE UNIVERSITY]

The Acid-catalyzed Reaction of Alkyl Azides upon Carbonyl Compounds[1]

BY J. H. BOYER AND J. HAMER[2]

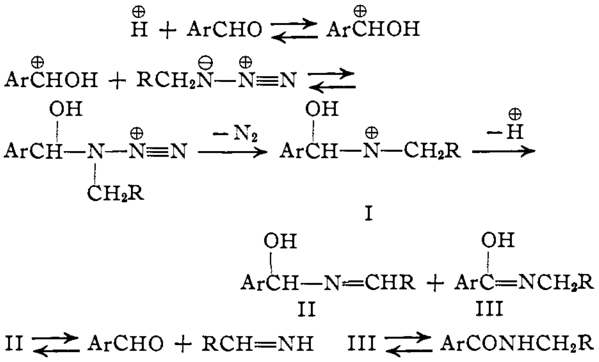
RECEIVED AUGUST 27, 1954

In an extension of the Schmidt reaction, amides were obtained from certain primary azides and aromatic aldehydes. The acid-catalyzed reaction at higher temperatures of β- and γ-azidohydrins with aromatic aldehydes brought about the formation of oxazolines and dihydroöxazines, respectively.

The literature has described certain similarities between aliphatic diazo compounds and their isosteric azides. Alkylation of aldehydes and ketones by diazomethane and the corresponding acid-catalyzed reaction of hydrazoic acid upon carbonyl compounds, also known as the Schmidt reaction, provide a good example. This report describes an extension of the latter reaction to alkyl azides.

Whereas diazoethane and higher homologs are more reactive than diazomethane toward carbonyl compounds,[3] alkyl azides are not capable of participation in a corresponding acid-catalyzed reaction on certain carbonyl compounds. Thus, no product was identified from the acid-catalyzed decomposition of methyl azide in the presence of benzoic acid.[4] Apparently methyl azide also failed to react with acetophenone since the only product identified from the reaction in the presence of sulfuric acid was acetanilide,[5] obtained in 2% yield.

A general reaction between alkyl azides and carbonyl compounds in the presence of a strong acid now has been demonstrated; from aromatic aldehydes the most encouraging results were obtained. A straight-forward adaptation of the currently accepted mechanism for the Schmidt reaction[5] and the alkylation of carbonyl compounds by diazoalkanes[6] provides an explanation for this new route to certain N-substituted amides and derivatives.



$$\overset{\oplus}{H} + \mathrm{ArCHO} \rightleftarrows \mathrm{Ar\overset{\oplus}{C}HOH}$$

$$\mathrm{Ar\overset{\oplus}{C}HOH} + \mathrm{RCH_2\overset{\ominus}{N}{-}\overset{\oplus}{N}{\equiv}N} \rightleftarrows \mathrm{Ar\overset{OH}{C}H{-}\underset{CH_2R}{N}{-}\overset{\oplus}{N}{\equiv}N} \xrightarrow{-N_2} \underset{\text{I}}{\mathrm{Ar\overset{OH}{C}H{-}\overset{\oplus}{N}{-}CH_2R}} \xrightarrow{-\overset{\oplus}{H}}$$

$$\underset{\text{II}}{\mathrm{Ar\overset{OH}{C}H{-}N{=}CHR}} + \underset{\text{III}}{\mathrm{Ar\overset{OH}{C}{=}NCH_2R}}$$

$$\text{II} \rightleftarrows \mathrm{ArCHO + RCH{=}NH} \qquad \text{III} \rightleftarrows \mathrm{ArCONHCH_2R}$$

The behavior of an alkyl azide as a weak Lewis base toward a carbonium ion is consistent with its reaction with the proton. In the latter case protonation is presumably the first step in the well-known acid-catalyzed decomposition of organic azides.[7] From a primary alkyl azide (RCH_2N_3) and the conjugate acid of an aldehyde, apparently an adduct was formed which subsequently underwent the loss of nitrogen, ejection of a proton and rearrangement either by a stepwise procedure such as the one described here or by an operation which would involve the simultaneous loss of nitrogen and the proton. Taft's rule that a carbonium ion loses a proton from the more electron-rich adjacent carbon atom,[8] was extended to the present system I. It was in excellent agreement with the experimental observation that the formation of amides either failed to occur altogether or occurred only to a minor extent with alkyl azides and aromatic aldehydes. This was to be expected, since amide formation involved removal of the proton from the aryl carbinol carbon atom (electron poor). On the other hand, removal of the proton from the adjacent alkyl carbon (electron rich) apparently resulted in the initial formation of a hydroxy Schiff base II and subsequent degeneration into an aldehyde and imine. The tautomeric shifts necessary to isomerize the hydroxy Schiff base II into the thermodynamically more stable amide modification are

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[2] Research Associate, 1953–1954.

[3] D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939).

[4] L. H. Briggs, G. G. DeAth and S. R. Ellis, *ibid.*, 61 (1942).

[5] P. A. S. Smith, THIS JOURNAL, **70**, 320 (1948).

[6] E. A. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 51.

[7] K. W. Sherk, A. G. Houpt and A. W. Brown, THIS JOURNAL, **62** 329 (1940); M. S. Newman and H. L. Gildenhorn, *ibid.*, **70**, 317 (1948); J. H. Boyer and F. C. Canter, *Chem. Revs.*, **54**, 1 (1954) P. A. S. Smith and B. B. Brown, THIS JOURNAL, **73**, 2438 (1951).

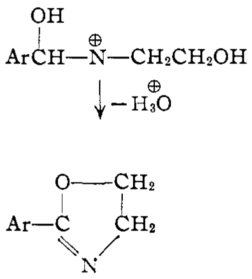
[8] R. W. Taft, Jr., *ibid.*, **70**, 3364 (1948).

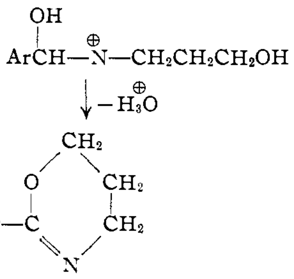
considered unlikely, in agreement with the demonstration that the acid-catalyzed change, $ArCH_2—N=CHR' \rightleftarrows ArCH=N—CH_2R'$, if it occurs at all is slow.[9]

Three simple primary alkyl azides were investigated in reactions with excess benzaldehyde and sulfuric acid. A low yield of N-β-phenylethylbenzamide was obtained from β-phenylethyl azide; however, there was no indication of amide formation from either *n*-butyl azide or benzyl azide. At lower temperatures the reactions between ethylene azidohydrin and benzaldehyde or *m*-nitrobenzaldehyde with sulfuric acid led to the formation of N-β-hydroxyethylbenzamide and N-β-hydroxyethyl-*m*-nitrobenzamide, respectively. Unidentified material was obtained from each azide reaction and was presumed to represent further reactions of decomposition products.

Confirmation of previously reported[4,5] observations that alkyl azides apparently failed to react with ketones and organic acids is in agreement with the suggested mechanism now proposed to explain amide formation from aldehydes and alkyl azides. Ejection of a proton from the adjacent carbinol carbon atom, a necessary requirement for amide formation, is, of course, impossible if the starting material is a carbonyl compound other than an aldehyde. Experiments with various monofunctional alkyl azides in acid-catalyzed reactions with cyclohexanone, acetophenone, benzophenone or benzoic acid led to the formation of intractable unidentified oily products together with recovered carbonyl compound. A few experiments on aliphatic aldehydes which contain hydrogen on the α-carbon also led to the formation of viscous oily products from which no single compound was isolated or identified. Those aliphatic aldehydes in which the α-carbon is tertiary are now being investigated.

Aliphatic azidohydrins also underwent similar reactions with aromatic aldehydes in which the course of events involved both functional groups. The acid-catalyzed reaction of β- and γ-azidohydrins on aromatic aldehydes at higher temperatures (see above) brought about the formation of Δ^2-oxazolines and dihydro-Δ^2-oxazines (the initial products may have been Δ^3-oxazolines and dihydro-Δ^3-oxazines), respectively, in high yields. In these cases, cyclization prior to or simultaneously with the ejection of the proton eliminated the possibility of the regeneration of the aldehyde with the formation of an aldimine.





From ethylene azidohydrin and each of seven ring-substituted derivatives of benzaldehyde, and from the similar reaction between benzaldehyde and 1-azido-2-propanol, the corresponding substituted oxazoline was obtained. Those aldehydes in which strong electron-releasing groups were substituted in positions *ortho* or *para* to the carbonyl atom gave a marked decrease in the efficiency of the reaction, as was to be expected from the corresponding decrease in the acidity of the respective conjugate acids. There was no significant change in the amount of oxazoline formation when the reactions between equimolar quantities of the azide and aldehyde with sulfuric acid were carried out in benzene, in which case two liquid phases were present.

The products obtained from ethylene azidohydrin in acid-catalyzed reactions with acetophenone, benzophenone and benzoic acid were not identified; however, it was established that neither oxazolines nor amides were present. The expected 2,2-disubstituted-Δ^3-oxazolines curiously enough are unknown. Exploratory experiments on the substitution of ethylene azidohydrin by azidoacetic acid and azidoacetone in acid-catalyzed reactions on benzaldehyde were unsuccessful.

Experimental[10]

Preparation of the Azides. ***n*-Butyl azide** was prepared according to the general procedure outlined by Henkel and Weygand[11] for alkyl azides. To a solution of 34.5 g. (0.53 mole) of sodium azide in 70 ml. of water and 35 ml. of methanol, 68.5 g. (0.50 mole) of *n*-butyl bromide was added at room temperature. The resulting mixture was heated on a steam-bath for 24 hours, during which time the bottom layer of butyl bromide disappeared as a top layer of butyl azide was formed and subsequently isolated in a separatory funnel. The crude azide was treated overnight at room temperature with an alcoholic solution of silver nitrate to remove the last traces of butyl chloride. After silver chloride was separated by filtration, the filtrate was washed with distilled water and then distilled. With practically no other fraction present there was obtained 40.0 g. (90%) of *n*-butyl azide, b.p. 106.5° (1 atm.), $n^{29.5}\text{D}$ 1.4152, $d^{29.5}$ 0.8649.

Anal. Calcd. for $C_4H_9N_3$: N, 42.39; *M*D, 28.49. Found: N, 42.62; *M*D, 28.87.

Methanol and butyl azide formed an azeotrope, b.p. 68°, from which the azide was liberated by the addition of a saturated solution of calcium chloride.

Combinations of *n*-butyl bromide and sodium azide without the use of an additional solvent did not lead to the formation of *n*-butyl azide.

***n*-Dodecyl azide**,[11] b.p. 170° (40 mm.), $n^{30}\text{D}$ 1.4441, 53% yield; **β-phenylethyl azide**,[12] b.p. 68° (0.5 mm.), $n^{26}\text{D}$ 1.5302, 65% yield; and **benzyl azide**,[13] b.p. 96° (43 mm.), 86% yield, were similarly prepared from corresponding halides and sodium azide in accordance with the previously reported procedures of other workers.

Ethylene azidohydrin, b.p. 75° (40 mm.), was prepared in 60% yield by heating a mixture of ethylene chlorohydrin and sodium azide on the steam-cone.[14] In an adaptation of this procedure, **3-azido-1-propanol** was prepared by heating 50 g. (0.36 mole) of 3-bromo-1-propanol (Eastman Kodak Co.) with 25 g. (0.38 mole) of sodium azide on a water-bath for 24 hours. The inorganic salts were removed by filtration and the filtrate was distilled. With no forerun, 18.5 g. (50% yield) of 3-azido-1-propanol was collected at 64° (2 mm.). Redistillation of the center cut provided an analytical sample, $n^{28}\text{D}$ 1.4569, $d^{27.5}$ 1.0802.

Anal. Calcd. for $C_3H_7N_3O$: C, 35.63; H, 6.98; N,

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[9] C. W. Shoppee, *Nature*, **162**, 619 (1948); K. von Auwers and H. Wienderling, *Ber.*, **65**, 70 (1932).

[10] Microanalyses by Micro-tech Laboratories, Skokie, Ill. Melting points are corrected; boiling points, uncorrected.

[11] K. Henkel and F. Weygand, *Ber.*, **76**, 812 (1943).

[12] P. A. S. Smith and B. B. Brown, THIS JOURNAL, **73**, 2437 (1951).

[13] T. Curtius and G. Ehrhart, *Ber.*, **55**, 1559 (1922).

[14] M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **93**, 1865 (1908).

TABLE I

SUBSTITUTED Δ^2-OXAZOLINES FROM RING-SUBSTITUTED DERIVATIVES OF BENZALDEHYDE AND ETHYLENE AZIDOHYDRIN

Substituted benzaldehyde	Substituted Δ^2-oxazoline	Yield, %	M.p., °C.	Molecular formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Nitrogen, % Calcd. Found	Picrate, m.p., °C.	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Nitrogen, % Calcd. Found
....	Phenyl	77	..[a]	C_9H_9NO	...	..	...	177[a]	...	..	...
					...	..	...		...	..	...
2-Hydroxy	2-(2-Hydroxyphenyl)	15	39	$C_9H_9NO_2$	66.24	5.56	8.59	158	45.92	3.08	14.29
					66.44	5.83	8.35		45.69	3.51	13.92
4-Hydroxy[b]	2-(4-Hydroxyphenyl)	25	187	$C_9H_9NO_2$	66.24	5.56	8.59	186	45.92	3.08	14.29
					66.16	5.62	8.36		46.35	3.11	14.21
2,4-Dihydroxy	2-(2,4-Dihydroxyphenyl)	Trace	..	$C_9H_9NO_3$	...	..	...				
					...	..	...				
4-Chloro	2-(4-Chlorophenyl)	75	85	C_9H_8NCl	59.51	4.44	7.71	190–191[c]	43.86	2.70	13.64
					59.64	4.50	7.52		44.01	2.88	13.58
4-Dimethylamino	2-(4-Dimethylaminophenyl)	10[d]	..	$C_{11}H_{14}N_2$	...	..	...	235–236	48.69	4.09	16.70
					...	..	...		48.66	4.25	16.78
4-Nitro	2-(4-Nitrophenyl)	70	180[e]	$C_9H_8N_2O_3$	56.25	4.19	14.58	169	42.76	2.63	16.63
					56.03	4.39	14.58		43.25	2.79	16.84
3-Nitro	2-(3-Nitrophenyl)[f]	73	119[g]	$C_9H_8N_2O_3$	...	..	...	143[g]	...	..	...
					...	..	...		...	..	...

[a] B.p. 240–243° (H. Wenker, THIS JOURNAL, **57**, 1079 (1935)). Recrystallization of the picrate derivative from aqueous solvents brought about the formation of the picrate derivative of β-aminoethyl benzoate, m.p. 198–199°.[25] *Anal.* Calcd. for $C_{15}H_{14}N_4O_9$: C, 45.69; H, 3.58; N, 14.21. Found: C, 45.76; H, 3.74; N, 13.92. [b] *p*-Hydroxybenzaldehyde was very insoluble in benzene. Five grams was dissolved in 100 ml. of benzene to which 10 ml. of concentrated sulfuric acid was added. [c] Recrystallization of the picrate derivative from aqueous solvents apparently brought about the formation of the picrate derivatives of β-aminoethyl *p*-chlorobenzoate, m.p. 176°. *Anal.* Calcd. for $C_{15}H_{13}N_4O_9Cl$: C, 42.02; H, 3.05; N, 13.07. Found: C, 41.64; H, 2.81; N, 12.73. [d] Based on product isolated as the picrate derivative. [e] M.p. 178.5° reported by R. Adams and M. T. Leffler, THIS JOURNAL, **59**, 2252 (1937). [f] The oxazoline was obtained from reactions carried out above 110°. At lower temperatures N-(β-hydroxyethyl)-*m*-nitrobenzamide, m.p. 134°, was obtained. [g] H. Elfeld, *Ber.*, **24**, 2319 (1891).

41.56; *M*D, 25.45. Found: C, 35.60; H, 7.05; N, 41.63; *M*D, 25.38.

1-Azido-2-propanol.—An attempt to prepare this azide by the method of Forster and Fierz[14] was unsuccessful. In an adaptation of the method of Henkel and Weygand,[11] 46.3 g. (0.49 mole) of 1-chloro-2-propanol (Eastman Kodak Co.), dissolved in 25 ml. of methanol and 50 ml. of water, was treated with 33 g. (0.51 mole) of sodium azide for 24 hours on the steam-bath. The mixture was separated in a separatory funnel and the upper layer distilled. The product, 28 g. (55% yield) of 1-azido-2-propanol, boiled at 53° (2.5 mm.), $n^{28}D$ 1.4525, d^{26} 1.0672.

Anal. Calcd. for $C_3H_7N_3O$: C, 35.63; H, 6.98; N, 41.56; *M*D, 25.38. Found: C, 35.08; H, 7.01; N, 40.50; *M*D, 25.61.

The reaction of propylene oxide with sodium azide was reported to give a mixture which was predominantly 1-azido-2-propanol[15] but which could not be purified for analysis and decomposed upon standing even in sealed ampoules. In contrast with these observations, samples of this azide prepared and purified by the present procedure have been stored in glass-stoppered bottles in the refrigerator for six months with no decomposition.

α-**Azidoacetic Acid.**—Forster and Fierz[16] prepared this compound by the saponification of ethyl azidoacetate and found that it was too unstable to be purified by distillation. An impure product also incapable of distillation now has been prepared from monochloroacetic acid and sodium azide. A mixture of 32 g. (0.34 mole) of monochloroacetic acid, 16 g. (0.33 mole) of sodium hydroxide and 23 g. (0.35 mole) of sodium azide in 100 ml. of water and 10 ml. of ether was heated on a steam-bath for 24 hours. The reaction mixture was then cooled and treated with ice-cold dilute sulfuric acid to liberate azidoacetic acid from its sodium salt. In ten ether extractions the azide was separated from the aqueous solution. The dried ether solution was then distilled to remove ether. Attempted further distillation of the residue, 14 g. (41% yield) was unsuccessful and brought about decomposition of the azido group. The product was used without further purification.

Azidoacetone, b.p. 38° (1 mm.),[17] $n^{20}D$ 1.4520,[17] was prepared from chloroacetone and sodium azide according to Forster and Fierz.[16]

Preparation of Amides. N-(β-Phenylethyl)-benzamide.—To a mixture of 50 ml. of redistilled benzaldehyde and 5 ml. of concentrated sulfuric acid, 3.0 g. (0.02 mole) of β-phenylethyl azide was added dropwise so that the temperature was held below 75°. Upon completion of gas evolution, benzaldehyde was removed from the mixture by distillation at reduced pressure. The residue was taken up in benzene, washed with sodium carbonate solution and with sodium bisulfite solution. Concentration, under vacuum, of the benzene solution left an oily residue which deposited a crystalline solid from ethanol. Upon recrystallization from ethanol-petroleum ether, colorless prisms of N-β-phenylethylbenzamide separated, m.p. 115.0°.[18] The yield was 0.48 g. (10%).

N-(β-Phenylethyl)-benzamide also was prepared from β-phenylethylamine and benzoyl chloride.[18] Its m.p. and the melting point of a mixture with the amide obtained from β-phenylethyl azide and benzaldehyde was 115°.

The substitution of ethylene azidohydrin for β-phenylethyl azide in the above directions led to the formation of N-(β-hydroxyethyl)-benzamide, m.p. 66–67°,[19] in low yield.

N-(β-Hydroxyethyl)-*m*-nitrobenzamide.—A mixture of 15 g. of *m*-nitrobenzaldehyde,[20] m.p. 58°, 3.0 g. (0.034 mole) of ethylene azidohydrin and 4.0 ml. of concentrated sulfuric acid was heated at 80–100° (see below) for 15 minutes or until gas evolution had ceased. Upon addition of 25 ml. of cold water, unreacted *m*-nitrobenzaldehyde precipitated and was separated by filtration. The addition of dilute alkali to the filtrate brought about the precipitation of amorphous brown-yellow solid. After three recrystallizations from water 4.5 g. (63% yield) of N-(β-hydroxyethyl)-*m*-nitrobenzamide, m.p. 134°, was obtained as a light-cream colored micro-crystalline solid.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.79; N, 13.33. Found: C, 51.25; H, 4.67; N, 13.46.

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(15) C. A. VanderWerf, R. Y. Heisler and W. E. McEwen, THIS JOURNAL, **76**, 1231 (1954).

(16) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **93**, 77 (1908).

(17) J. H. Boyer and D. Straw, THIS JOURNAL, **74**, 4506 (1952).

(18) A. Bischler and B. Napieralsky, *Ber.*, **26**, 1891 (1893).

(19) S. Frankel and M. Corneliu, *ibid.*, **51**, 1657 (1918); L. Knorr and P. Rossler, *ibid.*, **36**, 1278 (1903).

(20) This compound was prepared by the nitration of benzaldehyde according to A. Ehrlich, *ibid.*, **15**, 2010 (1882).

Preparation of Oxazolines.—Good yields of oxazolines from ethylene azidohydrin and aromatic aldehydes (all commercially available) resulted from the following procedure: To a mixture of 0.03 mole of the aromatic aldehyde in 50 ml. of benzene and 5 ml. of concentrated sulfuric acid, 2.6 g. (0.03 mole) of ethylene azidohydrin was added dropwise at a rate which kept the benzene gently boiling. After standing an additional five minutes with stirring, 50 ml. of ice-water was added. The water layer was separated and neutralized with sodium carbonate. The solid oxazolines were isolated by filtration, whereas the liquid phenyloxazoline was separated by ether extraction. The crude solid oxazoline was recrystallized from aqueous ethanol. Yields, physical constants and analytical data are in Table I.

Picrate derivatives (Table I) were prepared from ether solutions and recrystallized from ethanol and ethyl acetate.[21] The hydrochloride, m.p. 81°, of 2-phenyl-Δ^2-oxazoline[22] was prepared by bubbling anhydrous hydrogen chloride into an anhydrous ether solution of the amine.

Preparation of 2-Phenyl-Δ_2-dihydro-1,3-oxazine.—To a solution of 3.0 g. (0.03 mole) of benzaldehyde in 50 ml. of benzene and 5 ml. of concentrated sulfuric acid, 3.0 g. (0.03 mole) of 3-azido-1-propanol was added dropwise with stirring at a rate which kept the temperature at 80°. After standing five minutes with stirring, 50 ml. of ice-water was added. The water layer was separated, neutralized with sodium carbonate and extracted with ether. Evaporation of the ether left an oily residue. Distillation of this residue gave 3.5 g. (72%) of 2-phenyl-Δ_2-dihydro-1,3-oxazine, b.p. 115° (1.5 mm.).[23] The picrate, m.p. 151.5°,[24] was prepared in an ether solution.

Preparation of 5-Methyl-2-phenyl-Δ_2-oxazoline.—The above procedure was followed with the substitution of 1-azido-2-propanol for 1-azido-3-propanol. The product, 5-methyl-2-phenyl-Δ_2-oxazoline, b.p. 95° (0.5 mm.),[25] was obtained in 80% yield. Its picrate derivative, m.p. 166–167°,[25] was prepared from an ether solution.

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[21] Hydrolysis of oxazolines has long been known to lead to the formation of either β-hydroxyamides or β-aminoesters (R. H. Wiley and L. L. Bennet, Jr., *Chem. Revs.*, **44**, 447 (1949)). The latter generally are produced by the action of dilute acid upon an oxazoline. The ease with which this reaction may proceed was illustrated by the formation of the picrate of β-aminoethyl benzoate upon recrystallization of phenyloxazoline picrate from water. Apparently a similar transformation occurred in attempts to prepare and purify the picrate derivative of *p*-chlorophenyloxazoline.

[22] W. Wislicenus and H. Korber, *Ber.*, **35**, 164 (1902).

[23] T. Curtius and K. Thun, *J. prakt. Chem.*, **44**, 182 (1891).

[24] S. Gabriel, *Ber.*, **24**, 3214 (1891).

[25] S. Gabriel and T. Heyman, *ibid.*, **23**, 2479, 2499 (1890).

NEW ORLEANS 18, LA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

The Preparation and Structural Proof of Thiophene Amidone and Isoamidone

BY EDWARD A. SCHILDKNECHT AND ELLIS V. BROWN[1]

RECEIVED AUGUST 20, 1954

Heterocyclic analogs of amidone and isoamidone have been prepared in which the two phenyl groups have been replaced by two 2-thienyl groups. The structure of thiophene isoamidone has been proven, thus indicating the structure of the other isomer.

In view of the importance of amidone and isoamidone,[2] and the ever-present desire to obtain an analgesic of greater potency with the least number of side-effects, it seemed advisable to attempt the preparation of the thiophene analog of these two compounds. It was possible, on the basis of other investigations,[3] that these thiophene analogs might have greater analgesic activity, less toxicity or less tendency to cause addiction.

For this synthesis di-(2-thienyl)-acetonitrile was considered to be a useful intermediate; consequently, its preparation in good yields was investigated. Both stannic chloride and phosphorus pentoxide have been used as reagents in the condensation of mandelonitrile with benzene and its homologs.[4]

For the preparation of 2-benzylthiophene, zinc chloride has been used to condense benzyl alcohol with thiophene.[5] Our attempts to condense mandelonitrile with thiophene in the presence of stannic chloride, phosphorus pentoxide and zinc chloride have produced black tars.

Many reports have been published[6] concerning the condensation of carbonyl compounds with rhodanine. Such products are useful intermediates for the synthesis of substituted acetonitriles. The condensation of 2-benzoylthiophene with rhodanine has been attempted with negative results. Almost a quantitative amount of ketone was recovered.

Carboxylic acids and esters have long been known as intermediates for the preparation of nitriles through the corresponding amides. Therefore the preparation of di-(2-thienyl)-acetic acid was investigated. This compound has been reported by Blicke and Tsao,[7] who have prepared it, in low yield, by a synthesis involving many steps; other routes therefore were investigated. Diphenyl-2-thienylacetic acid has been prepared by the condensation of benzilic acid with thiophene in glacial acetic acid using concentrated sulfuric acid.[8] The condensation of benzilic acid with benzene has been reported in the presence of stannic chloride.[9] Attempts to condense mandelic acid with thiophene in the presence of these two reagents failed to produce the desired product.

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[2] C. C. Scott and K. K. Chen, *J. Pharmacol. and Exptl. Therap.*, **87**, 63 (1946); N. B. Eddy, C. F. Touchberry and J. E. Lieberman, *ibid.*, **98**, 121 (1950).

[3] A. M. Lands, V. L. Nash and K. Z. Hooper, *ibid.*, **86**, 129 (1946).

[4] H. Michael and J. Jeanpretre, *Ber.*, **25**, 1615 (1892).

[5] W. Steinkopf and W. Hanske, *Ann.*, **541**, 238 (1939).

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