[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF KANSAS]

On the Reactions of Certain Methylene Hydrogen Derivatives Containing Cyanide, Thiocyanate or Sulfinate Radicals

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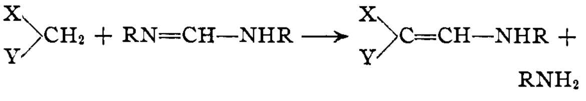
It has been shown previously in a series of papers[1] that compounds containing the methylene hydrogen grouping exhibit the characteristic property of reacting with disubstituted formamidines, forming a carbon to carbon linking and yielding an aminomethylene derivative which may be represented as follows



$$\begin{matrix}X\\Y\end{matrix}\!\!>CH_2 + RN{=}CH{-}NHR \longrightarrow \begin{matrix}X\\Y\end{matrix}\!\!>C{=}CH{-}NHR + RNH_2$$

These reactions occur in the case of open-chain compounds as acetoacetic ester, benzoylacetic ester, cyanoacetic ester, malonic ester and desoxybenzoin; also heterocyclic compounds as thiazolidones, pyrazolones, isoxazolones and imidazolones are similarly reactive.

The present investigation was carried out with methylene derivatives in which one group was a benzoyl or substituted benzoyl grouping and the other the CN, SCN or p-$CH_3C_6H_4SO_2$ radical, $(XC_6H_4COCH_2Y)$, in order to ascertain the effect of the latter groups on the reactivity of the methylene hydrogen with the formamidines and in a few cases with benzaldehyde and *p*-nitrosodimethylaniline.

The aminomethylene derivatives obtained in this study were found usually to react with hydrazine, phenylhydrazine and hydroxylamine yielding pyrazole or isoxazole derivatives. However, *p*-phenylanilinomethylenebenzoylacetonitrile failed to give such pyrazole or isoxazole compounds.

Experimental

I. Derivatives of Phenacyl Cyanide

Anilinomethylenebenzoylacetonitrile (III) $C_6H_5COC(CHNHC_6H_5)CN$.—Phenacyl cyanide (6 g.) and diphenylformamidine (8 g.) were heated in xylene solution at 120° for two hours. Anilinomethylenebenzoylacetonitrile (m. p. 159°) and aniline were formed.

Reactions of Anilinomethylenebenzoylacetonitrile with Hydroxylamine.—The nitrile (III) was refluxed in alcohol solution with hydroxylamine hydrochloride, either by itself, in pyridine solution or after neutralization with sodium carbonate. In all cases the same products were obtained, aniline and a compound (XI) melting at 154°, which was insoluble in hydrochloric acid and was recovered unchanged after solution in alkali. It cannot be the expected 2-phenyl-3-cyanoisoxazole which should in the presence of alkali rearrange to benzoylmalonic dinitrile.[2] The compound failed to react with phenylhydrazine, benzoyl chloride, and ethyl iodide and was hydrolyzed only after long boiling with 40% sodium hydroxide. These properties and its inertness point to the probable structure of 4-benzoyl-5-iminoisoxazole (XI) $ON{=}CHCH(COC_6H_5)C{=}NH$.

With hydrazine.—When this nitrile (III) was refluxed with hydrazine in alcoholic solution, 3-phenyl-4-cyanopyrazole (XII) (m. p. 134°) and aniline were formed.

With Phenylhydrazine.—The anilinomethylene derivative (III) reacted with phenylhydrazine in an analogous manner and gave aniline and 1,5-diphenyl-4-cyanopyrazole (XIII) (m. p. 182°). This product is soluble in most organic solvents but is practically insoluble in either acid or alkali.

Proof of Structure of 1,5-Diphenyl-4-cyanopyrazole.—This was accomplished by hydrolyzing the cyano group to a carboxylic group. Refluxing with 75% sulfuric acid, concentrated hydrochloric acid or sodium hydroxide failed to effect hydrolysis. Concentrated sulfuric acid at 130° hydrolyzed the compound to benzoic acid. The desired carboxylic acid was obtained by heating the pyrazole in a sealed tube with concentrated alcoholic potassium hydroxide at 160 to 170° for three hours, yielding 1,5-diphenyl-4-pyrazolecarboxylic acid (XIV) (m. p. 173°) and ammonia. This acid was found to be identical with that obtained by hydrolyzing the anilide of 1,5-diphenyl-4-pyrazolecarboxylic acid.

The fact that the phenylhydrazone of the phenacyl cyanide failed to react on heating with diphenylformamidine (two hours at 120°) points to this same structure.

4-Dimethylaminoanilinobenzoylacetonitrile (I) $C_6H_5COC({=}NC_6H_4N(CH_3)_2)CN$.—Nitrosodimethylaniline condensed readily with phenacyl cyanide in boiling alkaline alcoholic solution. The blood-red crystals from dioxane melted at 128°.[3]

II. *p*-Bromophenacyl Cyanide and Derivatives

***p*-Bromophenacyl Cyanide** (XV).—*p*-Bromophenacyl chloride (60 g.) was partially dissolved in alcohol (200 cc.). A solution of sodium cyanide (28 g.) was slowly added with continuous stirring, the mixture being cooled with ice. The mixture was then warmed to 60° and the stirring continued for one hour, the color changing from brown to reddish-violet. The cyanide was precipitated by acidifying and was deposited as slightly colored small thick plates (m. p. 159°).

Anilinomethylene-*p*-bromobenzoylacetonitrile (XVI) p-$BrC_6H_4COC({=}CHNHC_6H_5)CN$.—This resulted when

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[1] F. B. Dains, *et al.*, *Ber.*, **35**, 2496 (1902); THIS JOURNAL, **31**, 1148 (1909); **35**, 959, 970 (1913); **38**, 1510, 1841 (1916); **40**, 562 (1918); **43**, 613, 1200 (1921); **44**, 2310 (1922); *K. U. Sc. Bull.*, **15**, 265 (1924); **18**, 627 (1928).

[2] F. B. Dains and E. L. Griffin, THIS JOURNAL, **35**, 959 (1913).

[3] Lippmann, Diss., Berlin, 1905.

TABLE I

Text no.	Compound	Formula	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
I	4-Dimethylaminoanilinobenzoylacetonitrile	$C_{17}H_{15}ON_3$	128	15.16	15.05
II	Benzalphenacyl cyanide	$C_{16}H_{11}ON$	85	6.01	5.83
III	Anilinomethylenebenzoylacetonitrile	$C_{16}H_{12}ON_2$	159	11.29	11.23
IV	*p*-Bromoanilinomethylenebenzoylacetonitrile[a]	$C_{16}H_{11}ON_2Br$	205	8.56	8.38
V	*p*-Chloroanilinomethylenebenzoylacetonitrile[b]	$C_{16}H_{11}ON_2Cl$	185	9.91	9.91
VI	*o*-Chloroanilinomethylenebenzoylacetonitrile[c]	$C_{16}H_{11}ON_2Cl$	167	9.91	9.96
VII	*o*-Ethoxyanilinomethylenebenzoylacetonitrile[d]	$C_{18}H_{16}O_2N_2$	138	9.59	9.64
VIII	*p*-Phenoxyanilinomethylenebenzoylacetonitrile[e]	$C_{22}H_{16}O_2N_2$	135	8.24	8.38
IX	*p*-Phenylanilinomethylenebenzoylacetonitrile[f]	$C_{22}H_{16}ON_2$	161	8.64	8.53
X	1,3-Diphenyl-4-(*p*-bromoanilinomethylene-5-pyrazolone[g]	$C_{22}H_{16}ON_3Br$	184	Br, 19.14	19.14
XI	4-Benzoyl-5-iminoisoxazole[h]	$C_{10}H_8O_2N_2$	154	14.89	14.87
XII	3-Phenyl-4-cyanopyrazole[i]	$C_{10}H_7N_3$	134	24.84	24.41
XIII	1,5-Diphenyl-4-cyanopyrazole[j]	$C_{16}H_{11}N_3$	182	17.14	16.78
XIV	1,5-Diphenyl-4-pyrazolecarboxylic acid	$C_{16}H_{12}O_2N_2$	173	10.60	10.39
XV	*p*-Bromophenacyl cyanide	C_9H_6ONBr	159	6.25	6.27
				Br, 35.71	35.85
XVI	Anilinomethylene-*p*-bromobenzoylacetonitrile	$C_{16}H_{11}ON_2Br$	143	Br, 24.54	24.58
XVII	*p*-Bromoanilinomethylene-*p*-bromobenzoylacetonitrile	$C_{16}H_{10}ON_2Br$	209	Br, 39.41	39.26
XVIII	4-(4-Bromobenzoyl)-5-iminoisoxazole	$C_{10}H_7O_2N_2Br$	195	10.48	10.12
XIX	3-(4-Bromobenzoyl)-4-cyanopyrazole	$C_{10}H_6N_3Br$	195	Br, 32.26	32.11
XX	1-Phenyl-5-(4-bromophenyl)-4-cyanopyrazole	$C_{16}H_{10}N_3Br$	212	Br, 24.69	24.40
XXI	2-Imino-3-phenyl-5-benzoylthiazole	$C_{16}H_{12}ON_2S$	257	10.00	10.07
XXII	2-Imino-3-(4-bromophenyl)-5-benzoylthiazole[k]	$C_{16}H_{11}ON_2SBr$	214	7.80	7.97
				Br, 22.28	22.19
XXIII	2-Imino-3-(4-chlorophenyl)-5-benzoylthiazole[l]	$C_{16}H_{11}ON_2SCl$	204	8.90	8.89
XXIV	ω-Benzalphenacyl-*p*-tolyl sulfinate	$C_{22}H_{18}O_3S$	142	S, 8.86	9.18
XXV	Phenylhydrazone of phenacyl-*p*-tolyl sulfinate	$C_{21}H_{20}O_2N_2S$	188	7.69	8.06
				S, 8.81	8.66
XXVI	Anilinomethylenephenacyl-*p*-tolyl sulfinate	$C_{22}H_{19}O_3NS$	208	3.71	3.75
XXVII	*p*-Bromoanilinomethylenephenacyl-*p*-tolyl sulfinate[m]	$C_{22}H_{18}O_3NSBr$	210	3.07	3.05
				Br, 17.55	17.65
XXVIII	1,5-Diphenyl-4-(*p*-tolylsulfonyl)-pyrazole	$C_{22}H_{18}O_2N_2S$	164	7.49	7.93
XXIX	*p*-Chloroanilinomethylenephenacyl-*p*-tolyl sulfinate[n]	$C_{22}H_{18}O_3NSCl$	217	3.40	3.53
XXX	*o*-Chloroanilinomethylenephenacyl-*p*-tolyl sulfinate[o]	$C_{22}H_{18}O_3NSCl$	187	3.40	3.40
XXXI	Anilinomethylene-*p*-nitrobenzyl cyanide	$C_{15}H_{11}O_2N_3$	Above 260	15.85	15.63
XXXII	Anilinomethylene-*p*-nitrophenylacetic ethyl ester	$C_{17}H_{16}O_4N_2$	114–115	8.97	8.82

[a] Fusion of phenacyl cyanide with di-*p*-bromophenylformamidine.

[b] Fusion of phenacyl cyanide with di-*p*-chlorophenylformamidine.

[c] Fusion of phenacyl cyanide with di-*o*-chlorophenylformamidine.

[d] Fusion of phenacyl cyanide with di-*o*-ethoxyphenylformamidine.

[e] Fusion of phenacyl cyanide with di-*p*-phenoxyphenylformamidine.

[f] Fusion of phenacyl cyanide with di-*p*-xenylphenylformamidine.

[g] Fusion of 1,3-diphenyl-5-pyrazolone with di-*p*-bromophenylformamidine.

[h] From action of hydroxylamine on III, IV, V, VI, VII, VIII.

[i] From action of hydrazine on III, IV, V, VI, VII.

[j] From action of phenylhydrazine on III, IV, V, VI, VII, VIII.

[k] Fusion of phenacyl thiocyanate and di-*p*-bromophenylformamidine.

[l] Fusion of phenacyl thiocyanate and di-*p*-chlorophenylformamidine.

[m] Fusion of phenacyl-*p*-tolyl sulfinate and di-*p*-bromophenylformamidine.

[n] Fusion of phenacyl-*p*-tolyl sulfinate and di-*p*-chlorophenylformamidine.

[o] Fusion of phenacyl-*p*-tolyl sulfinate and di-*o*-chlorophenylformamidine.

(XV) and diphenylformamidine were fused at 150° and crystallized from benzene in white needles (m. p. 143°).

Reactions of Anilinomethylene-*p*-bromobenzoylacetonitrile.—This compound (and also *p*-bromoanilinomethylenebenzoylacetonitrile) reacted with hydroxylamine to give an isoxazole (XVIII) (m. p. 195°); with hydrazine to give a phenyl pyrazole (XIX) (m. p. 195°); and with phenylhydrazine to give a diphenyl pyrazole (XX) (m. p. 212°). Aniline (*p*-bromoaniline in the case of the bromine derivative) was the other product of these reactions.

III. Derivatives of Phenacyl Thiocyanate

2-Imino-3-phenyl-5-benzoylthiazole (XXI) $SC(NH)NC_6H_5CHCCOC_6H_5$.—Phenacyl thiocyanate (3.5 g.) and diphenylformamidine (4 g.) were heated at 160° in xylene for one hour. The product was washed with dilute acid and was crystallized from dioxane in fine light yellow crystals (m. p. 257°). Aniline was formed also in the reaction. Anilinomethylenephenacyl thiocyanate was doubtless formed first, but this evidently rearranged to a thiazole. It was not hydrolyzed with concentrated hydrochloric acid, sulfuric acid or alcoholic potassium hydroxide. No hydrolyzable sulfur was indicated by tests with lead plumbite. This derivative gave negative results for the presence of a free thiocyanate grouping in tests using alkaline lead tartrate.[4] It was unreactive to phenylhydrazine. These properties and the work of Kaufmann on thiocyanate derivatives[5] indicate such rearrangement.

Phenacyl thiocyanate was found to react also with di-*p*-bromophenylformamidine and di-*p*-chlorophenylformamidine to give analogous derivatives (XXII and XXIII).

IV. Derivatives of Phenacyl-*p*-tolyl Sulfinate

ω-Benzalphenacyl-*p*-tolyl Sulfinate (XXIV) $C_6H_5COC(CHC_6H_5)SO_2C_7H_7$.—Phenacyl-*p*-tolyl sulfinate and benzaldehyde (excess) were boiled in alcoholic solution to which had been added a few drops of piperidine. On cooling, small white crystals were deposited (m. p. 142°).

Phenacyl-*p*-tolyl sulfinate failed to react with *p*-nitrosodimethylaniline in an analogous manner.

Phenylhydrazone of Phenacyl-*p*-tolyl Sulfinate (XXV) $C_6H_5C(NNHC_6H_5)CH_2SO_2C_7H_7$.—Phenylhydrazine readily reacted with phenacyl-*p*-tolyl sulfinate to form the phenylhydrazone crystallizing in pale yellow short thick plates (m. p. 188°) from dioxane.

Anilinomethylenephenacyl-*p*-tolyl Sulfinate (XXVI) $C_6H_5COC(CHNHC_6H_5)SO_2C_7H_7$.—Phenacyl-*p*-tolylsulfinate (5 g.) and diphenylformamidine (5 g.) were heated together at 180 to 190° for one hour in xylene. The reaction product was washed with dilute acid to remove the aniline formed, and crystallized from dioxane in fine needles (m. p. 208°).

Di-*p*-bromophenylformamidine, di-*p*-chlorophenylformamidine and di-*o*-chlorophenylformamidine were found to react similarly with the sulfinate (derivatives XXVII, XXIX and XXX).

Reaction with Phenylhydrazine.—The anilinomethylene (XXVI) derivative reacted with phenylhydrazine when refluxed in alcoholic solution to give in small yield 1,5-diphenyl-4-(*p*-tolylsulfonyl)-pyrazole (XXVIII) (m. p. 164° from a mixture of alcohol and dioxane). This same pyrazole was obtained from *p*-bromoanilinomethylenephenacyl-*p*-tolyl sulfinate (XXVII) and phenylhydrazine.

Attempted Reactions with Hydrazine and Hydroxylamine.—The anilinomethylene (XXVI) and the *p*-bromoanilinomethylene (XXVII) derivatives failed to react with hydrazine or with hydroxylamine on refluxing in alcoholic solution.

V. Derivatives of *p*-Nitrobenzyl Cyanide and *p*-Nitrophenylacetic Ester

Anilinomethylene-*p*-nitrobenzyl Cyanide (XXXI) *p*-$NO_2C_6H_4C(CHNHC_6H_5)CN$.—This was prepared by fusing *p*-nitrobenzyl cyanide and diphenylformamidine. It formed fine orange-red needles from dioxane (m. p. above 260°). Aniline was split off in the reaction.

p-Nitrobenzyl cyanide was compared with benzyl cyanide in the ease of reaction with formamidines. The former derivative is much more reactive than benzyl cyanide, reacting readily and approaching phenacyl cyanide in reactivity.

The anilinomethylene derivative (XXXI) failed to react with hydroxylamine.

Anilinomethylene-*p*-nitrophenylacetic Ethyl Ester (XXXII) *p*-$NO_2C_6H_4C(CHNHC_6H_5)COOC_2H_5$.—*p*-Nitrophenylacetic ethyl ester and diphenylformamidine were fused together to yield this derivative. It was deposited from alcohol in long yellow needles (m. p. 114–115°). Aniline was split off in this reaction.

p-Nitrophenylacetic ethyl ester failed to react with *p*-nitrosodimethylaniline.

Summary

The methylene hydrogen reactions of phenacyl cyanide, *p*-bromophenacyl cyanide, *p*-nitrobenzyl cyanide, *p*-nitrophenylacetic ester, phenacyl thiocyanate and phenacyl-*p*-tolyl sulfinate with certain disubstituted formamidines have been studied and a number of new derivatives have been synthesized.

Phenacyl cyanide approaches benzoylacetic ester in methylene hydrogen reactivity as does also *p*-bromophenacyl cyanide and *p*-nitrobenzyl cyanide, while phenacyl thiocyanate is less reactive and phenacyl-*p*-tolyl sulfinate reacts with still more difficulty.

The anilinomethylene derivatives studied condense in nearly all the instances tried with hydroxylamine and the hydrazines to form isoxazoles and pyrazoles, respectively. Failures noted: *p*-phenylanilinomethylenebenzoylacetonitrile (no reaction with phenylhydrazine, hydrazine or hydroxylamine); anilinomethylenephenacyl-*p*-tolyl sulfinate (reacted with phenylhydrazine but not with hydrazine or hydroxylamine); *p*-bromoanilinomethylenephenacyl-*p*-tolyl sulfinate (reacted with phenylhydrazine but not with hydrazine or hydroxylamine); anilinomethylene-*p*-nitrobenzyl cyanide (no reaction with hydroxylamine).

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[4] See Söderbäck, *Ann.*, **443**, 156 (1925).

[5] Kaufmann, *Arch. Pharm.*, **266**, 197 (1928).