p-bromobenzoic acid, and the acid identified by the mixed melting point method. The mixed melting point method was also used to identify the solid product, 3,5-dibromoisobutyrylmesitylene. The total yield of *p*-bromotoluene was 21.9 g., or 68.4% of the theoretical. After a few recrystallizations from methanol, there remained 46.5 g. of the dibromo ketone melting at 69.5–71°, a yield of 71.5%.

Summary

The halogenation of hindered ketones by treatment with solutions of alkali hypohalites has been extended to include methyl, ethyl and isopropyl ketones as well as one 1,3-diketone.

The resulting α-halogen ketones have been described and certain reactions characteristic of the type have been studied.

Cleavage with alkali has been shown to be very difficult to effect. Only in the case of α,α,α-tribromoacetylmesitylene was the cleavage successfully carried out. In some cases the alkali acts as a dehalogenating agent.

It has been shown that these compounds are dehalogenated by treatment with phenol, *p*-halophenols being formed.

Dehalogenation has been effected also by treatment with the Grignard reagent. This reaction involves an interchange of radicals.

URBANA, ILLINOIS

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ALKYLATED DIKETOPYRAZOLIDINES AND TETRAKETOPYRAZOPYRAZOLES FROM ALKYLMALONIC ESTERS AND HYDRAZINE

BY ARTHUR W. DOX

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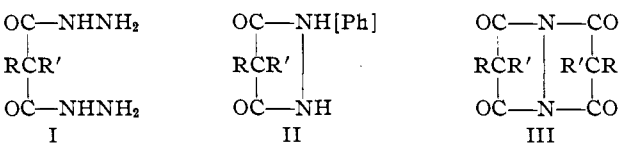
Condensations of alkylmalonic acid derivatives with hydrazines have thus far yielded three types of products.



Type I is the simple dihydrazide resulting from direct condensation between an alkylmalonic ester and hydrazine hydrate. A series of such dihydrazides has recently been prepared by de Graaf.[1]

Type II is represented by the "diethylmalonylhydrazine" which Einhorn and Feibelmann[2] obtained in the condensation of diethylmalonyl chloride with hydrazine; by the diethyl- and dipropyl-1-phenyl-3,5-"pyrazolidone" obtained by Conrad and Zart[3] from the dialkylmalonic esters and

[1] De Graaf, Dissertation, Leiden, 1930.

[2] Einhorn and Feibelmann, *Ann.*, **359**, 186 (1908).

[3] Conrad and Zart, *Ber.*, **39**, 2282 (1906).

phenylhydrazine in the presence of sodium ethoxide; and by the corresponding dimethyl derivative prepared by Michaelis and Schenk[4] from dimethylmalonic acid, *sym.*-acetylphenylhydrazine and phosphorus trichloride. More recently Kaufmann[5] obtained similar derivatives with substituents on both nitrogens by condensing diethylmalonyl chloride with symmetrically disubstituted hydrazines.

Type III represents a condensation between hydrazine and two alkylmalonyl groupings. Obviously only unsubstituted hydrazines, or hydrazines with easily detachable substituents could react in this manner. Two examples of type III have been described, namely, the tetraethyl and tetrapropyl derivatives prepared by Freund and Fleischer[6] by a reaction between the dialkylmalonyl chlorides and benzalsemicarbazone.

It is of interest to note that the two examples of type III contain dialkyl- rather than monoalkyl-malonyl groupings. In type II the dialkylmalonyl derivatives predominate. The only examples of type II with one substitution in the malonyl but none in the hydrazine grouping appear to be the benzyl and *m*-methylbenzyl derivatives described by Curtius.[7]

Experimental

The simplest procedure for effecting the ring condensation is that of Conrad and Zart,[3] which uses the ester of the malonic acid, and sodium ethoxide as the condensing agent. It is obviously an adaptation of the Fischer and Dilthey[8] barbituric acid synthesis. Its chief advantage lies in its use of esters which are much more readily available than acid chlorides. Conrad and Zart did not, however, apply the reaction to esters of monoalkylmalonic acids or to unsubstituted hydrazine.

The writer's interest in this reaction began with an attempt to determine the selectivity between the pyrazolidone and the barbituric acid condensations. Semicarbazide, for example, contains both hydrazine and urea groupings, and when condensed with a malonic ester might yield either a pyrazolidone-N-carboxamide or an isomeric N-aminobarbituric acid. Neither of these substances, however, was obtained. It appears that the semicarbazide first breaks down into biurea and hydrazine, the latter then condensing with the malonic ester.

From ethyl diethylmalonate and semicarbazide hydrochloride with sodium ethoxide in absolute alcohol two products were obtained and easily separated, one soluble and the other insoluble in sodium hydroxide. The first melted at 267° and the second at 263° with evolution of gas. The

[4] Michaelis and Schenk, *Ber.*, **40**, 3568 (1907).
[5] Kaufmann, *Z. angew. Chem.*, **40**, 69 (1927).
[6] Freund and Fleischer, *Ann.*, **379**, 27 (1910).
[7] Curtius, *J. prakt. Chem.*, **94**, 273 (1916).
[8] Fischer and Dilthey, *Ann.*, **333**, 334 (1904).

analyses agreed with values calculated for 4,4-diethyl-3,5-diketopyrazolidine and biurea, respectively.

	C	H	N
Alkali-sol. product: found	53.41	7.70	18.04
$C_7H_{12}O_2N_2$: calcd.	53.85	7.69	17.94
Alkali-insol. product: found	20.05	4.96	47.13
$C_2H_6O_2N_4$ (biurea): calcd.	20.34	5.08	47.46

Since biurea contains two urea groupings which failed to condense with the malonic ester it is apparent that unsubstituted hydrazine is more reactive.

In extending the hydrazine condensation to homologous alkylmalonic esters the interesting observation was made that disubstituted esters invariably yielded pyrazolones of type II, whereas monosubstituted esters invariably gave the double condensation represented by type III. In neither case could the types be interchanged by varying the proportions of the reacting substances. With a stable substituent on the hydrazine, as in phenylhydrazine, a double condensation is obviously precluded.

The following derivatives were prepared from the appropriate malonic esters and hydrazine monohydrochloride, or phenylhydrazine, by heating the mixture with alcoholic sodium ethoxide for five to seven hours in an

TYPE II

3,5-Diketopyrazolidines[9]	M. p., °C.	Formula	Found, % C	H	N	Calculated, % C	H	N
4,4-Diethyl	267	$C_7H_{12}O_2N_2$	54.10	7.89	18.01	53.85	7.69	17.94
4,4-Dipropyl	254	$C_9H_{16}O_2N_2$	58.54	8.75	15.26	58.69	8.70	15.22
4,4-Dibutyl	220	$C_{11}H_{20}O_2N_2$	62.36	9.56	13.40	62.26	9.43	13.21
4,4-Diisoamyl	289–290	$C_{13}H_{24}O_2N_2$	65.17	10.18	11.93	65.00	10.00	11.67
4-Ethyl-4-isoamyl	228	$C_{10}H_{18}O_2N_2$	60.01	9.14	14.32	60.61	9.09	14.14
4-Ethyl-4-hexyl	182	$C_{11}H_{20}O_2N_2$	61.49	9.38	13.05	62.26	9.43	13.21
4-*Sec.*-butyl-4-allyl	186–187	$C_{10}H_{16}O_2N_2$	60.84	7.90	14.31	61.22	8.16	14.29
4-Ethyl-4-phenyl	196–197	$C_{11}H_{12}O_2N_2$	64.66	5.98	13.61	64.70	5.88	13.73
4-Ethyl-1-phenyl	108	$C_{11}H_{12}O_2N_2$	64.02	6.13	13.36	64.70	5.88	13.73
4-*Sec.*-butyl-1-phenyl	94	$C_{13}H_{16}O_2N_2$	66.94	6.97	11.84	67.24	6.90	12.07
4,4-Diethyl-1-phenyl	114	$C_{13}H_{16}O_2N_2$	67.87	6.99	12.23	67.24	6.90	12.07

TYPE III

1,3,5,7-Tetraketopyrazo-[1,2-α] pyrazoles[10]								
2,6-Diethyl	246–247	$C_{10}H_{12}O_4N_2$	52.75	5.46	12.15	53.57	5.36	12.50
2,6-Dipropyl	278	$C_{12}H_{16}O_4N_2$	56.93	6.48	11.11	57.14	6.35	11.11
2,6-Di-*sec.*-butyl	207	$C_{14}H_{20}O_4N_2$	59.33	7.03	10.23	60.00	7.14	10.00

[9] Three of the above Type II pyrazolones have been previously described. Einhorn and Feibelmann[2] prepared the 4,4-diethyl derivative by a different method and report a melting point of 256°. Three different preparations of our product all melted at 267–268° corr. Conrad and Zart[3] prepared the 4,4-diethyl-1-phenyl derivative, m. p. 114–115°, and Michaelis and Schenk [*Ber.*, **41**, 3871 (1908)] the 4-ethyl-1-phenyl derivative, m. p. 105°, by a different method.

[10] The nomenclature of the Type III derivatives was kindly supplied by Dr. Austin M. Patterson.

oil-bath at 100–110°. The condensation product then present as the sodium salt was dissolved in water and precipitated by addition of hydrochloric acid, after shaking the alkaline solution with ether to remove any unreacted ester.

A tentative explanation of the difference in behavior between the monoalkyl- and dialkyl malonic esters is a possible enolization of the intermediate monoalkyldiketopyrazolidine which renders it capable of further reaction to form the pyrazopyrazole. This enolization would consist in a shifting of the 4-hydrogen to an adjacent carbonyl. The dialkyl derivatives, on the other hand, with no labile hydrogen in this position, could enolize only by a lactim–lactam tautomerism by which one of the nitrogens becomes tertiary and incapable of further reaction. The dialkyldiketopyrazolidine should therefore fail to condense with the ester of either a mono- or a dialkylmalonic acid. This was found to be the case.

Diethyldiketopyrazolidine and ethyl ethylmalonate were heated for seven hours at 100–105° with two equivalents of sodium dissolved in absolute alcohol. The clear homogeneous solution was then evaporated and the residue dissolved in water, shaken twice with ether to remove unreacted ester, and acidified. The crystalline product which separated melted at 267–268° and contained 18.03% N; calculated for $C_7H_{12}O_2N_2$, 17.94%; for $C_{12}H_{16}O_4N_2$, 11.11%. It consisted therefore of the original pyrazole and not the pyrazopyrazole derivative. The recovery was 77.4%.

The three pyrazopyrazole derivatives described above contain methylene hydrogens which are readily replaced by bromine. The reaction was performed by dissolving the substance in glacial acetic acid, adding a glacial acetic acid solution of bromine until a permanent yellow color was obtained, and then precipitating the product by addition of water.

2,6-Dibromo-1,3,5,7-tetraketo-pyrazo [1,2-α-] pyrazole	M. p., °C.	Formula	Br, % Found	Br, % Calcd.
2,6-Diethyl	171–173	$C_{10}H_{10}O_4N_2Br_2$	41.49	41.88
2,6-Dipropyl	138	$C_{12}H_{14}O_4N_2Br_2$	39.03	39.02
2,6-Di-*sec.*-butyl	111	$C_{14}H_{18}O_4N_2Br_2$	36.38	36.52

The alkyldiketopyrazolidines (Type II) are isomeric with the hydantoins, representing merely a transposition of one CONH grouping. They represent also the corresponding barbituric acids after removal of the urea carbonyl. Of special interest is the ethylphenyl derivative, which is Luminal without the urea carbonyl, and Nirvanol[11] transposed. Both of these drugs are potent hypnotics. Moreover, the pyrazoline structure suggests the possibility of antipyretic properties. Tests made by Dr. O. M. Gruhzit of this Laboratory showed some antipyretic properties, but the entire absence of hypnotic action. The pharmacological data will be published elsewhere.

[11] German Patent 309,508 (1918); Wernicke, *Deut. med. Wochschr.*, **42**, 1193 (1916).

Incidentally, the ethyl ethylphenylmalonate used in this preparation was obtained from a commercial source and contained some ethyl ethylphenylacetate. This accounts for a by-product obtained in the hydrazine condensation and readily separated by its insolubility in alkali. It melted at 218–219°.

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.07; H, 7.41; N, 8.64. Found [di-(ethylphenylacetyl) hydrazine]: C, 74.24; H, 7.36; N, 8.97.

Summary

A series of 4,4-dialkyl-3,5-diketopyrazolidines and of 2,6-dialkyl-1,3,5-7-tetraketopyrazo-[1,2-α]-pyrazoles has been prepared by condensing esters of alkylmalonic acids with hydrazine in the presence of sodium ethoxide.

The esters of dialkylmalonic acids yield the monocyclic pyrazolones, whereas those of monoalkylmalonic acids yield the dicyclic pyrazo-[1,2-α]-pyrazole derivatives.

DETROIT, MICHIGAN

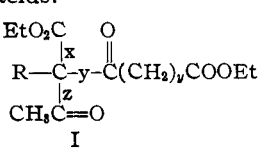
[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF WISCONSIN]

THE CLEAVAGE OF ALPHA-DIACYL AND OF ALPHA-MONOACYL BETA-KETO DERIVATIVES OF DIETHYL SUCCINATE, GLUTARATE AND ADIPATE

BY ROBERT NEVILL ISBELL, BRUNO WOJCIK AND HOMER ADKINS

RECEIVED MAY 9, 1932 PUBLISHED SEPTEMBER 5, 1932

It has been noted[1] in the hydrolysis of 1,3-diketones and β-keto esters of the types shown in formulas I and II, that cleavage and decarboxylation occurred in such a way as to produce more of the ketone RCH_2COCH_3 than of the keto acid $RCH_2CO(CH_2)_yCOOH$, from compounds of type I, and more of the keto acid $CH_3COCH_2(CH_2)_yCOOH$ than of $RCOCH_2(CH_2)_yCOOH$ from compounds of type II. That is to say, the removal of the acetyl group occurred to a less extent from compounds of type I, and to a greater extent from compounds of type II, than is desirable from the standpoint of the synthesis from acetoacetic ester of high molecular weight keto acids.



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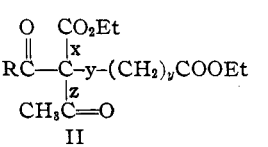

II

It may clarify the ensuing discussion if it is pointed out that compounds of these two types may upon hydrolysis cleave at three points

[1] G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 175 (1925); G. M. Robinson, *ibid.*, 745 (1930).