3,5-DIKETOPYRAZOLIDINE DERIVATIVES. I.

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When we try to obtain the acyl-derivatives of hydrazobenzene by substituting the hydrogen atoms attaching to the imino-groups in hydrazobenzene by acyl-groups, we sometimes obtain, as the results of the reaction, the derivatives of benzidine instead of those of hydrazobenzene. The difficulty to obtain the acyl-derivatives of the latter compound lies in the fact that the hydrazobenzene frequently undergoes benzidine transformation by various reagents.

D. Stern⁽¹⁾ carried out the reaction between hydrazobenzene and benzoyl chloride, and obtained contrary to his expectation dibenzoylbenzidine as a reaction product. In the case of the reaction between formic acid and hydrazobenzene, the analogous result was brought about, producing diformylbenzidine.

But several acyl-derivatives of hydrazobenzene are also obtained under suitable condition. For example, D. Stern obtained monoacetyl-hydrazobenzene under the action of acetic anhydride on hydrazobenzene, and also diacetyl-hydrazobenzene by heating the above two substances for a long time. C. A. Bischoff⁽²⁾ obtained various bromoacyl-compounds from α-bromofatty acids and hydrazobenzene. J. Biehringer and A. Busch⁽³⁾ produced monobenzoylhydrazobenzene by the action of benzoyl chloride on hydrazobenzene in alcohol in presence of slaked lime. H. P. Kaufmann⁽⁴⁾ prepared acylated hydrazobenzenes by the action of succinyl chloride and *o*-phthalyl chloride respectively on hydrazobenzene in dimethylaniline.

The author carried out the reaction between malonyl chloride and hydrazobenzene in the ether solution under cooling, and was able to isolate the colourless crystals, melt at 178°, by extracting the white precipitate, instantly produced in the ether solution, with petroleum ether.

On close inspection, this substance was proved to be a heterocyclic compound, namely, 1,2-diphenyl-3,5-diketopyrazolidine produced by substituting the hydrogen atoms of imino-groups in hydrazobenzene according to the following equation. Benzidine hydrochloride was simultaneously formed.

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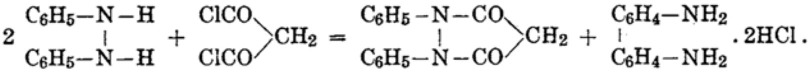
(1) Stern, *Ber.*, **17** (1884), 379.

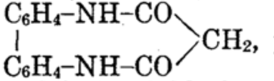
(2) Bischoff, *Ber.*, **31** (1898), 3241.

(3) Biehringer and Busch, *Ber.*, **36** (1903), 137.

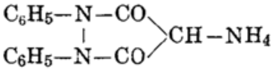
(4) Kaufmann, *Z. angew. Chem.*, **40** (1927), 69.



$$2\begin{array}{l}C_6H_5-N-H\\ \quad\ |\\ C_6H_5-N-H\end{array} + \begin{array}{l}ClCO\\ ClCO\end{array}\!\!>CH_2 = \begin{array}{l}C_6H_5-N-CO\\ \qquad\ |\\ C_6H_5-N-CO\end{array}\!\!>CH_2 + \begin{array}{l}C_6H_4-NH_2\\ |\\ C_6H_4-NH_2\end{array}.2HCl.$$

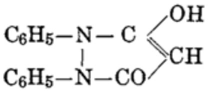
This compound forms colourless crystals and is soluble in alcohol, ether, acetone, chloroform and hot ligroin, while malonylbenzidine,  $\begin{array}{l}C_6H_4-NH-CO\\ |\\ C_6H_4-NH-CO\end{array}\!\!>CH_2$, prepared by Remfry⁽¹⁾ in 1911 has bluish gray colour, and is insoluble in almost all the ordinary organic solvents. The former bears some resemblance in its chemical properties to the derivatives of pyrazolone and pyrazolidone, especially to 1-phenyl-3,5-diketopyrazolidine described by Michaelis.⁽²⁾

It is insoluble in water, but soluble in alkali solution forming its salt. For example, the ammonium salt [1] is easily obtained as the colourless crystals, when the strong ammoniacal solution of diphenyl-diketopyrazolidine is evaporated up to dryness. M.p.: 138°–139°.



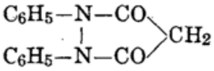
$$\begin{array}{l}C_6H_5-N-CO\\ \qquad\ |\\ C_6H_5-N-CO\end{array}\!\!>CH-NH_4 \qquad [1]$$

The constitution of diphenyl-diketopyrazolidine may be expressed as the enolic form [2], or the ketonic form [3], and the formation of salts may approve of the former formula.



$$\begin{array}{l}C_6H_5-N-C\overset{\diagup OH}{}\\ \qquad\ |\qquad\ \ \Vert\!>CH\\ C_6H_5-N-CO\end{array}$$

[2]



$$\begin{array}{l}C_6H_5-N-CO\\ \qquad\ |\\ C_6H_5-N-CO\end{array}\!\!>CH_2$$

[3]

But, the easiness with which diphenyl-diketopyrazolidine condenses with aldehydes, ketones and nitrous acid, as stated in the following, shows us the existence of a methylene group in this compound, the author, therefore, prefers the formula [3], and has expressed its ammonium salt as diketo-compound as above.

Diphenyl-diketopyrazolidine is fairly stable, and is not decomposed by dilute acid nor by alkali. From its alkali solution, it is reprecipitated as white crystals unaltered, after neutralizing the solution with acid. It seems to be decomposed by heating with conc. alcoholic potash solution, but neither hydrazobenzene nor benzidine can be detected in the decomposition product, which shows that the compound is not simply hydrolysed into its components.

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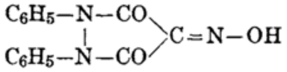
(1) Remfry, *J. Chem. Soc.*, **99** (1911), 621.

(2) Michaelis and Burmeister, *Ber.*, **25** (1892), 1502.

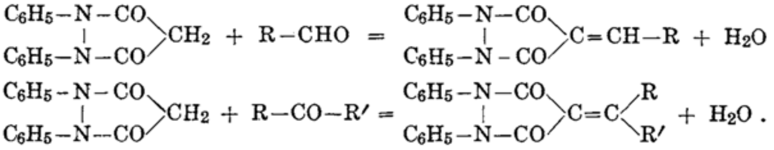
By the action of nascent nitrous acid, diphenyl-diketopyrazolidine forms isonitroso-compound; namely, 1,2-diphenyl-4-isonitroso-3,5-diketopyrazolidine [4].


[4]

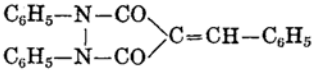
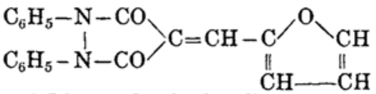
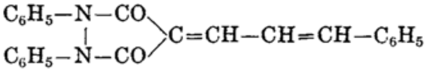
This compound contains two molecules of water of crystallization, and crystallizes in orange-red needles, while the anhydride forms dark red crystals and melts at 163°–164°.

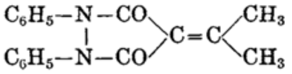
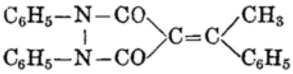
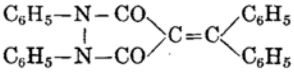
Diphenyl-diketopyrazolidine condenses with aldehydes and ketones forming various coloured substances. Its condensation with aldehydes is accomplished especially smoothly, and the products are obtained with good yields, only by heating the two components together on the water-bath for a short time; while its condensation with ketones requires more time and higher temperature.

At any late, the reactions with aldehydes and ketones are expressed by the following general formulae:—



The condensation products synthesised by the author are as follows.

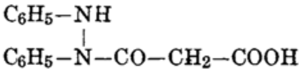
Aldehyde or ketone.	Condensation product.	M.p., °C.	Colour.
Benzaldehyde.	 [5] 1, 2-Diphenyl-4-benzylidene-3, 5-diketopyrazolidine.	164–165	Orange red.
Furfurol.	 [6] 1, 2-Diphenyl-4-furfurylidene-3, 5-diketopyrazolidine.	157–158	Dark red.
Cinnamaldehyde.	 [7] 1, 2-Diphenyl-4-cinnamylidene-3, 5-diketopyrazolidine.	190–192	Violet-tinged red.

Aldehyde or ketone.	Condensation product.	M.p., °C.	Colour.
Acetone.	 $\begin{array}{l} C_6H_5-N-CO \\ \quad\;\; \vert \\ C_6H_5-N-CO \end{array} > C=C < \begin{array}{l} CH_3 \\ CH_3 \end{array}$ [8] 1, 2-Diphenyl-4-isopropylidene-3, 5-diketopyrazolidine.	113	Canary yellow.
Acetophenone.	 $\begin{array}{l} C_6H_5-N-CO \\ \quad\;\; \vert \\ C_6H_5-N-CO \end{array} > C=C < \begin{array}{l} CH_3 \\ C_6H_5 \end{array}$ [9] 1, 2-Diphenyl-4-[α-phenylethylidene]-3, 5-diketopyrazolidine.	148–149	Yellow.
Benzophenone.	 $\begin{array}{l} C_6H_5-N-CO \\ \quad\;\; \vert \\ C_6H_5-N-CO \end{array} > C=C < \begin{array}{l} C_6H_5 \\ C_6H_5 \end{array}$ [10] 1, 2-Diphenyl-4-[diphenylmethylene]-3, 5-diketopyrazolidine.	269	Reddish yellow.

These products are easily decomposed by hot alkali solution, reproducing aldehydes or ketones.

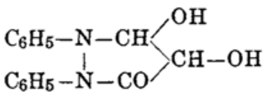
In addition to diphenyl-diketopyrazolidine, another substance of colourless needles was obtained from the ethereal part of the product of the above-mentioned reaction between malonyl chloride and hydrazobenzene. It dissolves in caustic soda solution, and is reprecipitated by the addition of acid. It is soluble in ordinary organic solvents, but insoluble in ligroin, and its constituent corresponds to the formula $C_{15}H_{14}O_3N_2$. M.p.: 160°–162°.

From its mode of formation, the constitution of this compound may be conjectured to be [11] or [12].



$$\begin{array}{l} C_6H_5-NH \\ \quad\;\; \vert \\ C_6H_5-N-CO-CH_2-COOH \end{array}$$

[11]



$$\begin{array}{l} C_6H_5-N-CH < \begin{array}{l} OH \\ \end{array} \\ \quad\;\; \vert \qquad\qquad\quad > CH-OH \\ C_6H_5-N-CO \end{array}$$

[12]

And if the former is true, it is expected that the compound will undergo the following decomposition on heating, forming azobenzene, acetanilide and carbon dioxide, in the same manner observed by Melms and others⁽¹⁾ on hydrazobenzene, or by Stern⁽²⁾ on monoacetyl-hydrazobenzene.

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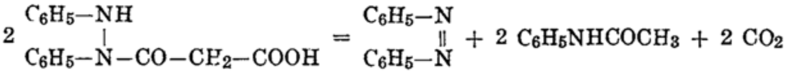
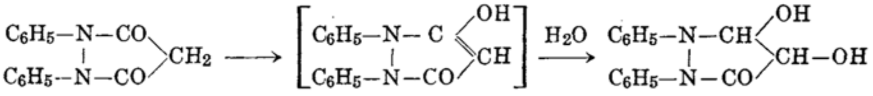
(1) Melms, *Ber.*, **3** (1870), 554; Lermontow, *Ber.*, **5** (1872), 235.

(2) Stern, *Ber.*, **17** (1884), 379.



$$2\begin{matrix}C_6H_5-NH \\ | \\ C_6H_5-N-CO-CH_2-COOH\end{matrix} = \begin{matrix}C_6H_5-N \\ \| \\ C_6H_5-N\end{matrix} + 2\ C_6H_5NHCOCH_3 + 2\ CO_2$$

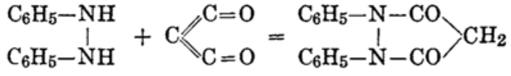
But in reality, nothing of these decomposition products could be detected. It is, therefore, presumed that the compound is [12], namely, the derivative of pyrazolidone, which undergoes complex decomposition under the influence of heat. Moreover, the same compound was produced when diphenyl-diketopyrazolidine, dissolved in the mixed solution of chloroform and alcohol, was allowed to stand for a few days after adding a few drops of dilute hydrochloric acid. In this case, diphenyl-diketopyrazolidine must be hydrated by the catalytic action of acid as in the following,



[3] [12]

On the other hand, the formation of [11] from diphenyl-diketopyrazolidine by hydrolysis with dilute hydrochloric acid is thought to be unprobable, as it is not hydrolysed into hydrazobenzene, as mentioned above, even with concentrated acid. In view of these facts, the compound in question is considered as [12], namely, 1, 2-diphenyl-3, 4-dihydroxy-5-pyrazolidone. It does not form isonitroso-compound with nitrous acid, as it has no methylene group in the molecule.

Parallel to the reaction between malonyl chloride and hydrazobenzene, the author carried out the reaction between carbon suboxide and hydrazobenzene, expecting that the reaction must be a suitable method for the preparation of diphenyl-diketopyrazolidine, as there is in this case no fear of benzidine transformation.



[3]

In fact, the same substances as were obtained by the action of malonyl chloride on hydrazobenzene, were also obtained in this case. But, the yields of them were very poor owing to the polymerization of the greater part of carbon suboxide into brownish black substance during the reaction.

Experimental Part.

A. The Reaction between Malonyl Chloride and Hydrazobenzene.

1,2-Diphenyl-3, 5-diketopyrazolidine, [3]. Malonyl chloride, used as a material for the reaction, was prepared principally according to the method described by Staudinger and Bereza.⑴

Fifty grams of powdered malonic acid and 160 gr. of thionyl chloride were heated in a flask under a reflux condenser for 60 hours at 40°, and then for 8 hours at 50°. The crystals of malonic acid went into solution forming the brownish liquid. It was then distilled under diminished pressure, and the fraction which boiled at 60° under 30 mm. pressure was collected as malonyl chloride.

A solution of 18.5 gr. of hydrazobenzene in 300 c.c. of ether was dropped from the tap-funnel into 200 c.c. of ether containing 10 gr. of malonyl chloride, and the white precipitate instantly produced in the flask was quickly filtered and well washed with ether, without exposing to moist air, as otherwise, the precipitate would change into a non-filterable viscous matter of brownish black colour. Diphenyl-diketopyrazolidine was obtained by extracting this precipitate with petroleum ether, and was recrystallized from ethyl alcohol. The yield was 6 gr. It crystallizes in colourless plates melting at 178°. It is insoluble in water and cold petroleum ether, but prettily soluble in alcohol and ether, and very soluble in acetone and chloroform. It dissolves in ammonia or in alkali solution, forming its salt.

Anal. Subst. = 0.1095; $CO_2 = 0.2862$; $H_2O = 0.0490$ gr. Found: C = 71.28; H = 5.01%. Calc. for $C_{15}H_{12}N_2O_2$: C = 71.41; H = 4.80%.

Subst. = 0.1850 gr.; $N_2 = 17.8$ c.c. (12°, 763 mm.) Found: N = 11.50%. Calc. for $C_{15}H_{12}N_2O_2$: N = 11.11%.

1, 2-Diphenyl-3, 4-dihydroxy-5-pyrazolidone, [12]. The ethereal filtrate, obtained by filtering the above-mentioned precipitate by the reaction between malonyl chloride and hydrazobenzene, was washed with water to decompose the excess of malonyl chloride remained in the solution. It was then shaken with an one percent solution of sodium carbonate. The soda solution gave a light yellow precipitate when acidified with hydrochloric acid. The precipitate was dissolved in the least quantity of chloroform, and alcohol was added to it, and the solution was allowed to stand for one day. From this solution, 1,2-diphenyl-3,4-dihydroxy-5-pyrazolidone crystallized in colourless needles. It melts at 160°–162°. Before melting it seems to be somewhat decomposed. It is soluble in ether and chloroform, sparingly soluble in alcohol, ligroin and water.

Anal. Subst. = 0.1204; $CO_2 = 0.2956$; $H_2O = 0.0550$ gr. Found: C = 66.94; H = 5.08% Calc. for $C_{15}H_{14}O_3N_2$: C = 66.67; H = 5.18%.

Subst. = 0.1454 gr.; $N_2 = 12.8$ c.c. (13°, 761 mm.) Found: N = 10.45%. Calc. for $C_{15}H_{14}O_3N_2$: N = 10.37%.

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(1) Staudinger and St. Bereza, *Ber.*, **41** (1908), 4463.

The same compound was obtained from 1, 2-diphenyl-3, 5-diketopyrazolidine by dissolving the latter in the mixed solution of chloroform and alcohol, and allowing it to stand for a few days after the addition of a small quantity of dilute hydrochloric acid.

B. The Reaction between Carbon Suboxide and Hydrazobenzene. According to the method of Staudinger and Bereza,(1) dibromomalonic acid was treated with phosphorus pentachloride in ether, and the liquid which boiled at 74°–75° under 17 mm. pressure was collected as dibromomalonyl chloride; and was used as a material for the preparation of carbon suboxide.

To the flask containing 30 gr. of zinc granules, 450 c.c. of ether solution containing 45 gr. of dibromomalonyl chloride was added from the tap-funnel, and the evolved carbon suboxide gas and the vapour of ether were introduced to a condenser which was connected to another flask containing the ethereal solution of 20 gr. of hydrazobenzene and cooled with freezing mixture. A small amount of white precipitate was produced in the ethereal solution. 1,2-Diphenyl-3,5-diketopyrazolidine was obtained from this precipitate when recrystallized from petroleum ether. Hydrogen chloride gas was then passed through the ethereal solution in order to precipitate the excess of hydrazobenzene as benzidine hydrochloride. The ethereal solution was washed with water, and evaporated up to dryness, and the reddish brown residue was washed with petroleum ether to remove azobenzene included in it. A small amount of colourless needles was obtained from this brownish residue when recrystallized from alcohol, and this compound was proved to be identical with diphenyl-dihydroxypyrazolidone obtained from malonyl chloride and hydrazobenzene.

C. The Derivatives of 1,2-Diphenyl-3,5-diketopyrazolidine. *Ammonium salt of 1, 2-diphenyl-3, 5-diketopyrazolidine*, [1]. When the ammonical solution of diphenyl-diketopyrazolidine was allowed to stand in a vacuum desiccator furnished with soda lime till the solution was evaporated to dryness, the ammonium salt was remained as the colourless crystals. M.p.: 138°–139°.

Anal. Subst. = 0.1262 gr.; $N_2 = 17.1$ c.c. (18.5°, 762 mm.) Found: N = 15.70%. Calc. for $C_{15}H_{15}O_2N_3$: N = 15.61%.

1,2-Diphenyl-4-isonitroso-3,5-diketopyrazolidine, [4]. To the caustic potash solution of 2 gr. of diphenyl-diketopyrazolidine, 0.6 gr. of sodium nitrite was added, and the excess of dilute hydrochloric acid was dropped

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(1) Staudinger and St. Bereza, *Ber.*, **41** (1908), 4461.

to this solution under cooling. Isonitroso-compound was deposited out at once as a yellow precipitate, which gave the long needle crystals of orange colour on recrystallization from hot water. The yield was 0.5 gr. It contains two molecules of water of crystallization, and the anhydrous compound has dark red colour and melts at 163°–164°. It is soluble in alcohol, benzene, ether and hot water, but insoluble in ligroin.

Anal. Subst.=0.0253; lost at 100°=0.0029 gr. Found: H_2O=11.5%. Calc. for $C_{15}H_{11}O_3N_3 \cdot 2H_2O$: H_2O=11.4%.

Subst.=0.1424 gr.; N_2=16.7 c.c. (20.5°, 763 mm.) Found: N=13.47%. Calc. for $C_{15}H_{11}O_3N_3 \cdot 2H_2O$: N=13.25%.

1,2-Diphenyl-4-benzylidene-3,5-diketopyrazolidine, [5]. When 2.5 gr. of diphenyl-diketopyrazolidine and 2 gr. of benzaldehyde were heated on the water-bath, the former dissolved into the latter forming a dark red solution, which solidified on cooling to a dark red mass. It was pressed on a porous plate, and washed with alcohol until it smelt no longer of benzaldehyde. The yield was 2.8 gr. The compound has orange red colour, and melts at 164°-165°. It is very soluble in chloroform, moderately soluble in alcohol and ether, but insoluble in ligroin. By the action of hot caustic alkali, it is decolourized and decomposed into its components.

Anal. Subst.=0.1581 gr.; N_2=12.0 c.c. (26°, 764 mm.) Found: N=8.57%. Calc. for $C_{22}H_{16}O_2N_2$: N=8.24%.

1,2-Diphenyl-4-furfurylidene-3,5-diketopyrazolidine, [6]. When 2 gr. of diphenyl-diketopyrazolidine was heated with 1.6 gr. of furfurol on the water-bath for a while, a reddish brown mass was obtained. It was pressed on a porous plate, and washed quickly with alcohol to remove furfurol still adhering to it. The condensation product was left in an almost pure state. The yield was 2 gr. It was once more purified by dissolving it in alcohol and allowing it to stand after the addition of petroleum ether. The compound crystallized out as dark red prisms. It melts at 157°–158°; and is soluble in acetone, benzene and ether. but insoluble in water.

Anal. Subst.=0.1513 gr.; N_2=11.6 c.c. (26°, 763 mm.) Found: N=8.65%. Calc. for $C_{20}H_{14}O_3N_2$: N=8.48%.

1,2-Diphenyl-4-cinnamylidene-3,5-diketopyrazolidine, [7]. 2.5 gr. of diphenyl-diketopyrazolidine and 2.5 gr. of cinnamaldehyde were mixed and heated on a water bath for one hour. The mixture solidified to a dark red mass, which was purified by washing with petroleum ether and alcohol, and dried on a porous plate. The yield was 3 gr. It has a violet-tinged red colour, and is soluble in alcohol, ether and chloroform, sparingly soluble in ligroin, but insoluble in water. M.p.: 190°–192°. Before melting it seems somewhat to decompose.

Anal. Subst.=0.1490 gr.; N_2=10.2 c.c. (26°, 763 mm.) Found: N=7.72%. Calc. for $C_{24}H_{18}O_2N_2$: N=7.65%.

1,2-Diphenyl-4-[α-phenylethylidene]-3,5-diketopyrazolidine, [9]. Two grams of diphenyl-diketopyrazolidine and 2 gr. of acetophenone were heated for one hour at 130°–180°. On cooling, the product solidified to a reddish brown viscous matter contaminating the yellow needle crystals. It was washed with ligroin, and on recrystallization from alcohol, it gave yellow needles, which melts at 148°–149°. The yield was 0.8 gr. It is soluble in ether and hot alcohol, but insoluble in water.

Anal. Subst.=0.0070 gr.; N_2=0.451 c.c. (23°, 764 mm.) (Pregl's method). Found: N=7.38%. Calc. for $C_{23}H_{18}O_2N_2$: N=7.91%.

1,2-Diphenyl-4-[diphenylmethylene]-3,5-diketopyrazolidine, [10]. Two grams of diphenyl-diketopyrazolidine and 2.8 gr. of benzophenone were fused together on the water-bath for one hour and a half and on a wire gauze, above 100°, for 1/2 hour. The product was extracted with alcohol, and this solution gave reddish yellow needle crystals when allowed to stand for one day. They were recrystallized once from alcohol. M.p.: 265°. The yield was 0.8 gr.

Anal. Subst.=0.0112 gr.; N_2=0.666 c.c. (23°, 758 mm.) (Pregl's method). Found: N=6.75%. Calc. for $C_{28}H_{20}O_2N_2$: N=6.73%.

In conclusion the author wishes to acknowledge his indebtedness to the Department of Education for a grant which has defrayed a part of the expense of this investigation.

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