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# Action of Hydrazines on Substituted 3,5-Pyrazolidinediones

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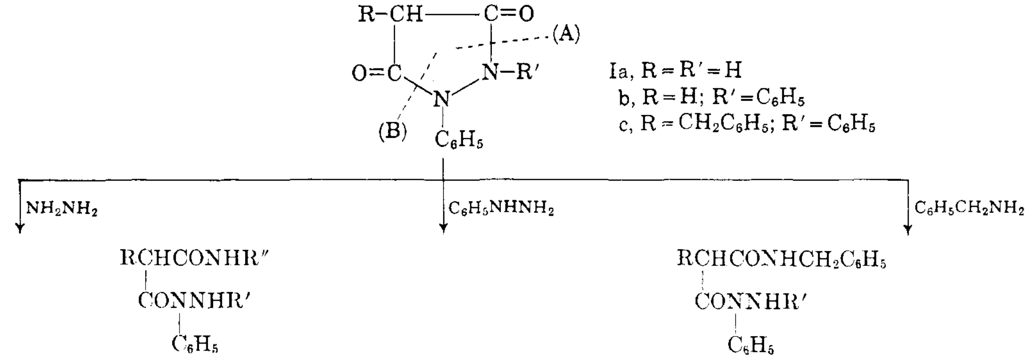
*Received December 27, 1960*

The heterocyclic ring in substituted 3,5-pyrazolidinediones now has been found to be opened by the action of hydrazines and/or benzylamine with the formation of mixed malonic hydrazides (*cf.* Scheme A).

Whereas, the action of hydrazine hydrate in absence of solvent effects the opening of the hetero-ring in 4-benzylidene-1,2-diphenyl-3,5-pyrazolidinedione, its action in pyridine solution results in the formation of VIII (*cf.* Scheme B). The latter is also obtained by the action of benzaldehyde hydrazones on 1,2-diphenyl-3,5-pyrazolidinedione.

Recently,[1] it has been shown that the exocyclic double bond of the highly colored 4-methyl-substituted 1-phenyl-3,5-pyrazolidinedione (VIIa) is reactive and adds organomagnesium compounds to give the colorless derivatives of 4-methyl-1-phenyl-3,5-pyrazolidinediones.

We now have extended the study of the behavior of the heterocyclic ring in 3,5-pyrazolidinediones (Ia–c), and it was found that the heterocyclic ring is readily opened[2] when Ia–c are allowed to react with hydrazine hydrate, phenylhydrazine, and/or benzylamine. The reaction products are believed to be mixed malonic hydrazides IIa–f and IIIa–c (*cf.* Scheme A).



Ia, $R = R' = H$
b, $R = H$; $R' = C_6H_5$
c, $R = CH_2C_6H_5$; $R' = C_6H_5$

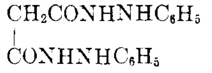
IIa. $R = R' = R'' = H$
b. $R = R'' = H$; $R' = C_6H_5$
c. $R = CH_2C_6H_5$; $R' = C_6H_5$; $R'' = H$
IId. $R = R' = H$; $R'' = C_6H_5$
e. $R = H$; $R' = R'' = C_6H_5$
f. $R = CH_2C_6H_5$; $R' = R'' = C_6H_5$

IIIa. $R = R' = H$
b. $R = H$; $R' = C_6H_5$
c. $R = CH_2C_6H_5$; $R' = C_6H_5$

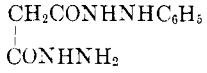
Scheme A

The assigned structure for the products IIa–f, is inferred from the fact that they are colorless. IIa–b react readily, in the cold, with benzaldehyde to give the corresponding benzylidene derivatives[3] (IVa–b). The infrared spectra of IIa–f show well defined absorption bands at 3450 cm.$^{-1}$ and 3350 cm.$^{-1}$ characteristic for the $NH_2$ and NH groups respectively. That phenylhydrazine effects the opening of bond (A) and not (B) (*cf.* Formula I), is shown by the nonidentity of IId with the already known V.[4] By analogy, the proposed structure for IIa is preferred to the possible isomeric structure VI.

The hydrazide structure for the product IIa described by Michaelis[2] and later by van Alphen[5] now has been proved.


$\begin{array}{l} CH_2CONHNHC_6H_5 \\ | \\ CONHNHC_6H_5 \end{array}$

V


$\begin{array}{l} CH_2CONHNHC_6H_5 \\ | \\ CONHNH_2 \end{array}$

VI

Treatment of IIb with boiling acetic anhydride results in the elimination of the hydrazine residue accompanied by ring closure and formation of Ib.

The behavior of 1-phenyl- and 1,2-diphenyl-4-benzylidene-3,5-pyrazolidinedione (VIIa–b) now has been investigated. Thus, when VIIa–b were treated with hydrazine hydrate in the cold and in absence of solvent, IVa–b were obtained respectively (*cf.* Scheme B). On the other hand, treat-

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[1] A. Mustafa, M. Kira, and M. El-essawi, *J. Org. Chem.*, **25**, 34 (1960).

[2] *Cf.* the stability of the heterocyclic ring in Ia toward the action of alkalies, A. Michaelis and R. Burmeister, *Ber.*, **25**, 1502 (1892).

[3] *Cf.* J. Blanksma and H. de Graef, *Rec. trav. chim.*, **57**, 3 (1938).

[4] M. Freund and B. Goldschmidt, *Ber.*, **21**, 1241 (1888).

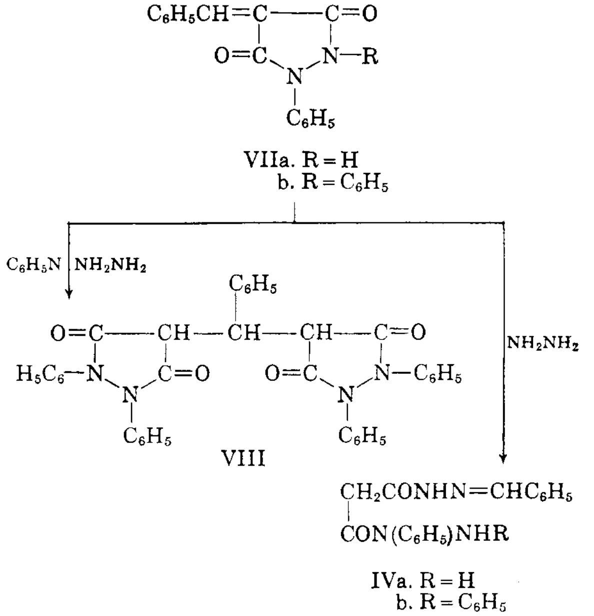
[5] J. van Alphen, *Rec. trav. chim.*, **43**, 853 (1924).

TABLE I

Mixed Malonic Acid Hydrazides and Related Compounds

| Reaction Product | Reaction |  |  | Recrystallization Solvent | M.P.[b] | Formula | Carbon |  | Hydrogen |  | Nitrogen |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  | Solvent[a] | Temp. | Time |  |  |  | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| IIa | — | 20 | 24 hr. | A | 140 | $C_9H_{12}O_2N_4$ | 51.92 | 51.87 | 5.76 | 5.68 | 26.92 | 26.91 |
| IVa |  |  |  | A | 215 dec. | $C_{16}H_{16}O_2N_4$ | 64.86 | 65.06 | 5.41 | 5.69 | 18.88 | 18.85 |
| IIb | — | 20 | 24 hr. | A | 151 | $C_{15}H_{16}O_2N_4$ | 63.39 | 63.22 | 5.62 | 5.52 | 19.72 | 19.93 |
| IVb |  |  |  | Ac | 202 dec. | $C_{22}H_{20}O_2N_4$ | 70.97 | 70.76 | 5.37 | 5.57 | 15.05 | 15.07 |
| IIc | — | 20 | 24 hr. | M | 105 | $C_{22}H_{22}O_2N_4$ | 70.58 | 70.97 | 5.88 | 6.13 | 14.97 | 14.65 |
| IId | A | 100 | 30 min. | A | 166 dec. | $C_{15}H_{16}O_2N_4$ | 63.36 | 63.46 | 5.63 | 5.80 | 19.71 | 19.56 |
| IIe | B | 100 | 30 min. | A | 188 dec. | $C_{21}H_{20}O_2N_4$ | 70.00 | 69.45 | 5.55 | 5.65 | 15.55 | 15.65 |
| IIf | B | 100 | 30 min. | A | 203 dec. | $C_{28}H_{26}O_2N_4$ | 74.66 | 74.75 | 5.77 | 6.01 | 12.44 | 12.55 |
| IIIa | A | 100 | 30 min. | A | 146 | $C_{16}H_{17}O_2N_3$ | 67.84 | 67.89 | 6.00 | 6.22 | 14.84 | 14.68 |
| IIIb | B | 100 | 30 min. | Ch-A | 185 | $C_{22}H_{21}O_2N_3$ | 73.53 | 73.59 | 5.84 | 6.06 | 11.69 | 11.45 |
| IIIc | A | 100 | 30 min. | B | 181 | $C_{29}H_{27}O_2N_3$ | 77.51 | 77.35 | 6.01 | 5.80 | 9.35 | 9.64 |

[a] A = alcohol; B = benzene; Ac = acetone; M = methanol; Ch = chloroform. [b] All melting points are corrected.



Scheme B

ment of the orange colored 4-*p*-methoxy-benzylidene-1,2-diphenyl-3,5-pyrazolidinedione with hydrazine hydrate results in the discharge of the color which reappears on acidification with the recovery of the starting material. The behavior of VIIb toward the action of hydrazine hydrate in presence of ethyl alcohol or pyridine seems to differ from its behavior toward the same reagent in absence of the solvent, resulting in the formation of VIII (*cf.* Scheme B). Similarly VIII was obtained when VIIb was treated with phenylhydrazine or with semicarbazide hydrochloride in pyridine. In the latter case benzaldehyde semicarbazone was isolated from the reaction mixture.

The ready reactivity of VIIa–b toward hydrazine hydrate in absence of solvent may parallel the behavior of 4-arylidene-5-isoxazolone[6] toward the action of phenylhydrazine.

One possible approach to explain the formation of IVa–b, is the assumption of the elimination of the arylidene group in position 4 with the intermediate formation of benzaldehyde hydrazone together with Ia–b. The latter will react spontaneously with hydrazine hydrate as shown above to give the intermediate IIa–b, which *via* the condensation with benzaldehyde hydrazone leads to the formation of IVa-b. It has now been found that IIb reacts readily with benzalazine to give a quantitative yield of IVb. In favor of this assumption is the fact that benzaldehyde phenylhydrazone now has been isolated from the reaction mixture of VIIa and phenylhydrazine under the same experimental conditions.

In a similar manner, the formation of VIII could be explained *via* the interaction of the intermediately formed benzaldehyde hydrazone, phenylhydrazone and/or semicarbazone, and Ib. Benzaldehyde azine, phenylhydrazone and/or semicarbazone now have been found to react with 1,2-diphenyl-3,5-pyrazolidine-dione (Ib) to give good yields of VIII. The structure assigned to VIII was confirmed by two independent syntheses. Thus, treatment of the monosodium derivative of Ib with benzal chloride and/or the addition of Ib to VIIb in presence of sodium ethoxide, led to the formation of VIII. The latter method is an example of the addition of an active methylene group to VIIb, which will be the subject of a forthcoming publication. The formation of VIII parallels the reaction of one mole of benzaldehyde with two moles of 1-phenyl-3-methyl-5-pyrazolone[7] depending on the conditions of the reaction.

The interaction of Ia–b with *p*-methoxybenzaldehyde hydrazone may be used for the preparation of 4-*p*-methoxybenzylidene derivatives of Ia–b respectively. In a similar manner 4-cyclohexylidene- and 4-isopropylidene-1,2-diphenyl-3,5-pyrazolidinediones now have been obtained by the action of cyclohexanone and/or acetone semicarbazones on Ia–b.

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(6) R. Fusco and C. Musante, *Gazz. chim. ital.*, **67**, 248 (1937); *Chem. Abstr.*, **31**, 8534 (1937).

(7) L. Knorr, *Ann.*, **238**, 137 (1887); J. Tambor, *Ber.*, **23**, 864 (1900).

Heating a solution of VIIb with *p*-methoxybenzaldehyde hydrazone results in the replacement of the benzylidene group by the *p*-methoxybenzylidene group with the formation of 4-*p*-methoxybenzylidene-1-phenyl-3,5-pyrazolidinedione. The study of the scope and mechanism of the above mentioned reactions is under further investigation.

## EXPERIMENTAL

*Action of hydrazines and/or benzylamine on* Ia–c.[8] *General procedure.* Equimolar amounts of the substituted 3,5-pyrazolindinedione derivatives (Ia–c) and hydrazine hydrate, phenylhydrazine, and/or benzylamine were allowed to react under the given experimental conditions (*cf.* Table I) to give the reaction products IIa–c, IId–f, and IIIa–c, respectively. They were obtained in an almost quantitative yield, and were readily crystallized from the proper solvent (*cf.* Table I).

The benzylidene derivatives (IVa–b) were obtained by treating a solution of one gram of each of the hydrazides (IIa–b) in ethanol (50%; 20 ml.) with the calculated amount of benzaldehyde.[8]

*Action of hydrazine hydrate on* VIIa–b.[9] One-half ml. (0.01 mole) of hydrazine hydrate was added to 2.64 g. (0.01 mole) of VIIa and the reaction mixture was allowed to stand at room temperature overnight, whereby the red color of VIIa was completely discharged. On the addition of 5% acetic acid (*ca.* 10 ml.) to the reaction mixture, a colorless solid separated. It was collected and upon crystallization from ethanol, gave colorless plates (*ca.* 1.5 g.), m.p. 215° dec. They were proved to be identical with IVa (m.p., mixed m.p. determinations, and infrared spectral comparisons; *cf.* Table I).

Similarly VIIb was treated with hydrazine hydrate to give colorless needles from acetone (80% yield), m.p. 202° dec., not depressed when mixed with a sample of IVb (*cf.* Table I).

*Action of hydrazine hydrate, phenylhydrazine, and/or semicarbazide hydrochloride on* VIIb. The following illustrates the general procedure. To a suspension of VIIb (3.41 g.; 0.01 mole) in 8 ml. pyridine was added with shaking 0.5 ml. (0.01 mole) of hydrazine hydrate. The red suspension dissolved slowly with discharge of color. After standing for about 30 min. at room temperature, the solution was acidified with 40 ml. of 30% acetic acid. The precipitated solid was collected, washed with little water, and crystallized from ethanol. Recrystallization from chloroform-ethanol mixture gave colorless plates (2.5 g.), m.p. 205° dec.

*Anal.* Calcd. for $C_{37}H_{28}O_4N_4$: C, 74.99; H, 4.73; N, 9.46 Found: C, 74.45; H, 4.81; N, 9.48.

They were identified as VIII (m.p. and mixed m.p. determinations; *cf.* below).

*Action of azines, hydrazones, and/or semicarbazones on* Ia–b. The following illustrates the general procedure. To a boiling solution of 2.52 g. (0.01 mole) of Ib in 10 ml. benzene was added 1.04 g. (0.005 mole) of benzalazine, whereby a crystalline product was formed within a few minutes. Heating (steam bath) was continued for further 10 min. After cooling to room temperature, the solid (2.5 g.) obtained was crystallized from chloroform-ethanol mixture as colorless plates, m.p. 205° dec.; they were identified as VIII (m.p. and mixed m.p. determinations).

Similarly treatment of a solution of Ia in acetic acid with *p*-methoxybenzaldehyde hydrazone gave a quantative yield of VIIc. It crystallized from chloroform ethanol mixture as orange needles, m.p. 246° dec., which proved to be identical with a sample of 1-phenyl-4-*p*-methoxybenzylidene-3,5-pyrazolidinedione prepared after Ascher.[9]

VIId was obtained in an 80% yield from Ib and *p*-methoxybenzaldehyde hydrazone in chloroform. It gave orange needles from chloroform-ethanol mixture, m.p. 199° dec., and was identified as 1,2-diphenyl-4-*p*-methoxybenzylidene-3,5-pyrazolidinedione (m.p. and mixed m.p. determinations with an authentic specimen[9]).

4-Cyclohexylidene- and 4-isopropylidene-3,5-pyrazoliolidinediones were prepared from cyclohexanone and acetone semicarbazone (50% and 20% yields), respectively. They crystallized from ethanol in form of yellow needles, m.p. 174° and 113°, respectively and were found identical with authentic samples prepared after Tsumaki.[9]

*Action of benzalazine on* IIb. A boiling solution of 2.84 g. (0.01 mole) of IIb in ethanol (15 ml.) was treated with 1.04 (0.005 mole) of benzalazine as shown above. The separated product (3 g.) was crystallized from acetone, m.p. 202° dec. and was found identical with IVb (m.p. and mixed m.p. determinations; *cf.* Table I).

*Synthesis of* VIII. *Method* (a), *Condensation of* Ib *with benzal chloride.* To a boiling solution of 5.04 g. (0.02 mole) of Ib in 80 ml. absolute alcohol was added a solution of sodium ethoxide (prepared from 0.46 g. sodium in 10 ml. absolute alcohol). The reaction solution was stirred for about 30 min. followed by the addition of 1.61 g. (0.01 mole) of freshly distilled benzal chloride. Heating at reflux temperature, with stirring, was continued for about 18 hr. Most of the alcohol was then distilled over, the solution cooled to room temperature and about 50 ml. of 5% sodium hydroxide were added. The insoluble sodium salt of VIII was collected, washed with little cold water and crystallized from acetic acid. Recrystallization from chloroform-ethanol mixture gave colorless plates (2.5 g.), m.p. 205° dec.

*Method* (b) *Addition of* Ib *to* VIIb. To a cold stirred solution of the sodium derivative of Ib (5.04 g., 0.02 mole) in 80 ml. absolute alcohol, prepared as shown above, was added 6.82 g. (0.02 mole) of 1,2-diphenyl-4-benzylidene-3,5-pyrazolidinedione (VIIb). Stirring was continued at room temperature for about 30 min., during which time the red suspension of VIIb was completely dissolved with discharge of color. The pale yellow alcoholic solution was concentrated to its half volume, cooled to room temperature, and acidified with 4 ml. of 50% acetic acid. The deposited crystalline product (9 g.) was recrystallized from chloroform-ethanol mixture, m.p. 205° dec.

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(8) For the preparation of Ia, *cf.* M. Conrad and A. Zart, *Ber.*, **39,** 2283 (1906); Ib, H. Ruhkopf, *Ber.*, **73,** 820 (1940); Ic, Brit. Patent **646,597** (Nov. 22, 1950); *Chem. Abstr.*, **45,** 7602 (1951).

(9) For the preparation of VIIa, *cf.* Th. Ascher, *Ber.*, **30,** 1018 (1897); VIIb, *cf.* T. Tsumaki, *Bull. chem. soc. Japan*, **7,** 45 (1932); *Chem. Abstr.*, **26,** 2977 (1932).