INVESTIGATIONS IN THE FIELD OF PYRAZOLIDINE CHEMISTRY

XIV. Influence of Enolization on the Stability of the N—N Bond of the 3,5-Dioxopyrazolidine Ring*

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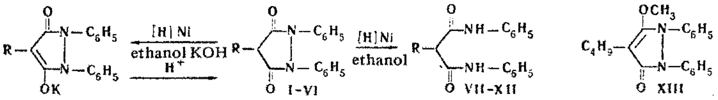
On hydrogenation in neutral ethanolic solution in the presence of a Raney nickel catalyst, 1,2,4-trisubstituted 3,5-dioxopyrazolidines undergo hydrogenolysis at the N—N bond. The enolate anions of these compounds and the fixed enolic form are stable to hydrogenolysis.

According to the molecular diagram of 3,5-dioxopyrazolidine [2] the N—N bond is the most highly strained bond of this ring. In actual fact, the cleavage of this bond has been observed repeatedly in the catalytic hydrogenation of dioxopyrazolidine derivatives in the presence of Raney nickel, i.e., in this case the dioxopyrazolidines behave as acid hydrazides [5]. However, the hydrogenation of dioxopyrazolidines in the presence of Raney nickel with retention of the heterocycle has been described in a number of patents [6].

In view of this it appeared to us to be of interest to study the behavior of various dioxopyrazolidines on hydrogenation in neutral and alkaline solution in order to attempt to connect the stability of the N—N bond of the ring with the position of the keto–enol or lactim–lactam equilibrium of these compounds.

This paper gives the results of a study of the hydrogenation of 4-substituted 3,5-dioxo-1,2-diphenylpyrazolidines (I–VI), the commonest group of compounds, some representatives of which are used in medicine.

Compounds I–VI were hydrogenated in neutral ethanolic solution at 20 and 60° C and in alkaline ethanolic solution at 20° C. In addition, the behavior of these compounds when their neutral ethanolic solutions were boiled in the presence of the catalyst was studied.



I, VII R = H; II, VIII R = C_2H_5; III, IX R = n-C_4H_9; IV, X R = C_6H_5; V, XI R = $(C_2H_5)_2NCH_2CH_2$; VI, XII R = $C_6H_5CH_2$

It was found that, in neutral ethanol, hydrogenolysis of the N—N bond takes place in all the 4-monosubstituted compounds I–VI with the formation of the corresponding malondianilides **VII–XII**. In alkaline ethanolic solution, no hydrogenolysis took place, and on acidification the starting materials **I–VI** were recovered unchanged in quantitative yields. Only in the case of compounds **IV** and **V** was a small amount of the product of the hydrogenolysis of the N—N bond detected by chromatography.

From the results obtained it is possible to draw the quite definite conclusion that the N—N bond of the pyrazolidines **I–VI** have increased stability when hydrogenated in alkaline solution. The reason for this may be either the influence of the alkali on the catalyst or the greater stability of the enolate anion as compared with the enolic or diketonic form. The first assumption is excluded by the fact that, as we have found, the O-methyl ether of 4-butyl-3,5-dioxo-1,2-diphenylpyrazolidine (**XIII**), which exists in the fixed enolic form, is not hydrogenated in neutral ethanolic solution at 20° C. 4-n-Butyl-4-methyl-3,5-dioxo-1,2-diphenylpyrazolidine (**XIV**), which exists in the fixed diketo form, on being hydrogenated in neutral ethanolic solution, like compounds **I–VI**, forms the corresponding dianilide **XV**. In alkaline ethanolic solution compound **XIV** is unstable and decomposes first at the N—C bond, giving butylmethylmalonmono(diphenylhydrazide) (**XVI**). The latter compound hydrogenates at the N—N bond with the formation of butylmethylmalonmonoanilide (**XVII**).

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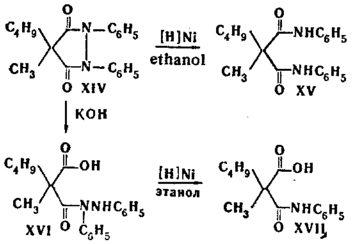
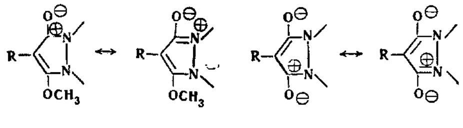
*For part XIII, see [1].



The increase in the stability of the N—N bond of the enolate anions and of the fixed enolic forms of the 1,2,4-trisubstituted, 3,5-dioxopyrazolidines can be explained by the contribution of the aromatic structures.



EXPERIMENTAL

The starting materials **I–VI** and **XIV** were obtained by methods to which references have been given in a previous paper |7|. Compound **XIII** was synthesized as described by Hammond et al. |8|.

Type W-5 Raney nickel catalyst |9| was used.

General hydrogenation procedure. A solution of 0.001 mole of the initial compound in 20 ml of ethanol was hydrogenated at normal pressure in the presence of 1 g of catalyst for 3 hr. The reaction was carried out in a round-bottomed flask with shaking in an "apparatus for shaking liquids in vessels" at 127 oscillations per minute. The filtrate, after removal of the catalyst and its washing with ethanol, was evaporated to dryness, and the products were obtained with yields of 75–100%. Samples of the filtrate, and of the residue after evaporation, were chromatographed in a thin layer (1 mm) of alumina on glass plates with dimensions of 12 × 12 mm by the ascending method in the presence of the starting material and the corresponding dianilide as reference samples. The detection of the spots of the substances was carried out in ultraviolet light (UB-1 ultrachemiscope) and in iodine vapor. The melting points of the starting materials **I–VI** and of the hydrogenation products **VII–XII**, the conditions for their chromatography, and the R_f values of the spots detected are given in the table.

Melting Points and Conditions for the Chromatographic Separation of Compounds I–XV

Starting material			Hydrogenolysis product			Chromatographic conditions	
compound	mp, °C	R_f×100	compound	mp, °C	R_f×100	alumina	solvent system
I	178	52	VII	223—224[10]	80	Grade II	Ethanol-25% ammonia (15 : 2)
II	108	50	VIII	213—215[11]	90	Grade II containing 2% CH_3COOH	Ethanol-25% ammonia (15 : 2)
III	104—105	15	IX	193[4]	85	Grade II containing 2% CH_3COOH	Benzene-ethanol (1: 1)
IV	184—185	5	X	201—202[12]	90	Grade II	Ethyl acetate
V	228—230	5	XI	153	90	Grade II	Ethyl acetate
VI	133—134	20	XII	221—222[13]	90	Grade II	Benzene-methanol (1 : 1)
XIII	84—85	50				Grade II containing 2% CH_3COOH	Benzene-chloroform (1: 3)
XIV	112	70	XV	195—196	35	Grade II	*

*Chromatographed first in the methanol-25% ammonia (4 : 1) system, with a run of half the plate. After the chromatogram had been dried in the usual way, chromatography was continued in the benzene-heptane (4 : 1) system.

When compounds **I–VI** were hydrogenated in neutral ethanolic solution at 20 and 60° C, and also when they were boiled with the catalyst for 3 hr (without a supply of hydrogen), substances with melting points close to those of the corresponding dianilides **VII–XII** were obtained. Under these conditions a single spot of the hydrogenolysis product was generally found on the chromatogram, and in some cases, a spot of the starting material as well.

On hydrogenation under similar conditions at 20° C, compound **XIII** was recovered unchanged from the solution in quantitative yield.

When compounds **I–VI** were hydrogenated at 20° C in alkaline ethanolic solution, 0.003–0.004 mole of KOH was used per 0.001 mole of the substance, and no hydrogen was absorbed.* After the separation of the catalyst, the filtrate was acidified with 8% HCl and diluted with water, the starting materials being recovered quantitatively.

Diethylaminoethylmalondianilide (XI). After 0.25 g of compound V had been boiled in 20 ml of ethanol in the presence of 1 g of Raney nickel for 3 hr, the catalyst was separated off, the ethanol was distilled off, and water was added to the residue to give 0.2 g of colorless crystals of a substance with mp 152–153° C showing a single spot on chromatography (see table). Found, %: N 12.15. Calculated for $C_{21}H_{27}N_3O_2$, %: N 11.89. IR spectrum (ν, cm^{-1}): 3200, 3180, 3145, 3090, 1668, 1610, 1554, 1505.

n-Butylmethylmalondianilide (XV). After 0.25 g of compound **XIV** had been hydrogenated in 20 ml of neutral ethanol in the presence of 1 mg of Raney nickel catalyst for 2 hr and the filtrate had been worked up in the manner described above, a colorless crystalline substance was obtained with mp 195–196° C, chromatographically homogeneous (see table). Found, %: N 8.48. Calculated for $C_{20}H_{24}N_2O_2$, %: N 8.64. IR spectrum (ν, cm^{-1}), 3347, 3223, 3129, 1657, 1600, 1554, 1531, 1500.

n-Butylmethylmalonmonoanilide (XVII). Compound **XIV**, 1.25 g, was hydrogenated in alkaline ethanolic solution in the presence of 4 g of catalyst at 20° C for 3 hr. After the separation of the catalyst, the filtrate was neutralized and evaporated to a small volume. The precipitate that deposited was purified by reprecipitation with acid from alkaline solution. This gave a colorless crystalline substance with mp 108–109° C. Found, %: N 5.90; equiv. 261.0. Calculated for $C_{14}H_{19}NO_3$, %: N 5.62; equiv. 249.3. IR spectrum (ν, cm^{-1}): 1688, 1637, 1587, 1539, 1488.

The IR spectra were recorded from mulls in paraffin oil with NaCl and LiF prisms.

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*It was established by means of preliminary experiments with compound **III** that one equivalent of KOH is insufficient to increase the stability of the N—N bond.