

Studies on Cyclopropanes

I. Preparation and Properties of Some Hexasubstituted Cyclopropanes

GUNNEL WESTÖÖ

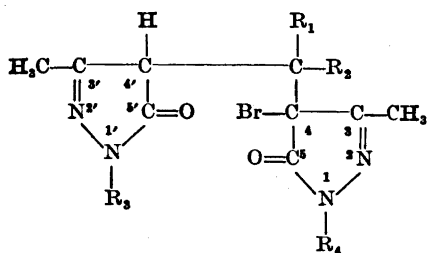
Institute of Organic Chemistry, University of Lund, Lund, Sweden

Alkali salts of 4-bromo-4,4'-isopropylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (I a) and related compounds, *e.g.*, I b—f, in solution are rapidly converted to hexasubstituted cyclopropanes, II a—f. These cyclopropane derivatives under proper conditions isomerize quantitatively to bispyrazolones of the structure III a, b or substituted III a, b, cleavage of the cyclopropane ring with migration of a hydrogen atom from a methyl group taking place.

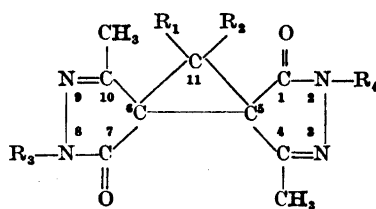
In a preceding paper¹ it was shown that 1,1',1''-triphenyl-3,3',3''-trimethyl-4-bromo-[4,4',4''-ter-2-pyrazoline]-5,5',5''-trione (IV) splits off hydrogen bromide with formation of furlone yellow (V) in good yield. The isomeric cyclopropane derivative was not detected among the reaction products and could only have been formed in a small amount, in spite of the fact that the analogous reaction between *e.g.*, 1-phenyl-3,4-dimethyl-4-bromo-2-pyrazolin-5-one and 1-phenyl-3,4-dimethyl-2-pyrazolin-5-one takes place with formation of a C—C bond, 1,1'-diphenyl-3,3'-dimethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione being formed². Besides for steric reasons, the non-appearance of a carbon-carbon coupling in the case of IV may be caused by a lack of electrons in the 4 and 4'' positions.

Experiments have now been performed to investigate whether an exchange of the second pyrazolonylidene group in IV for small, electron-releasing groups will cause formation of substituted cyclo-alkanes. Preparations of cyclopropane derivatives by ring closure of halogen compounds having an active hydrogen atom in the γ -position of the halogen atom have been described by several authors³⁻⁵.

The sodium salt of 4-bromo-4,4'-isopropylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (I a) could be prepared by a Michael addition of the sodium salt of 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one to 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one (VI a) in ethanol solution (equilibrium reaction, *cf.* Westöö^{1, 6, 7}). The addition compound rapidly splits off sodium bromide with formation of a neutral product of the empirical formula $C_{23}H_{22}N_4O_2$.

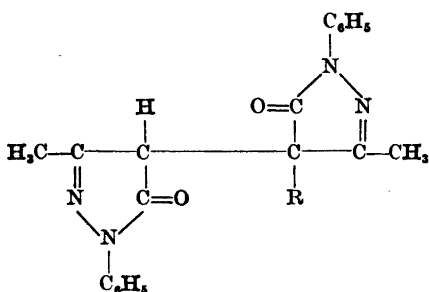


I

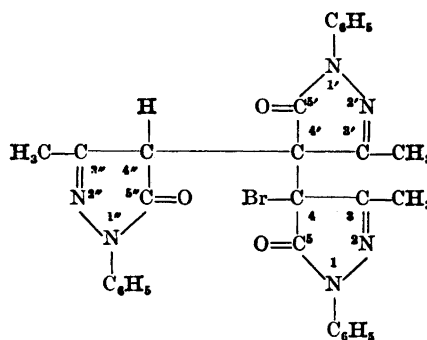


II

- a. $R_1 = R_2 = \text{CH}_3$; $R_3 = R_4 = \text{C}_6\text{H}_5$.
 b. $R_1 = R_2 = \text{CH}_3$; $R_3 = \text{C}_6\text{H}_5$; $R_4 = p\text{-CH}_3\text{C}_6\text{H}_4$.
 c. $R_1 = R_2 = \text{CH}_3$; $R_3 = \text{C}_6\text{H}_5$; $R_4 = p\text{-BrC}_6\text{H}_4$.
 d. $R_1 = \text{CH}_3$; $R_2 = \text{C}_2\text{H}_5$; $R_3 = R_4 = \text{C}_6\text{H}_5$.
 e. $R_1 = \text{CH}_3$; $R_2 = \text{C}_2\text{H}_5$; $R_3 = \text{C}_6\text{H}_5$; $R_4 = p\text{-CH}_3\text{C}_6\text{H}_4$.
 f. $R_1 = \text{CH}_3$; $R_2 = \text{C}_2\text{H}_5$; $R_3 = \text{C}_6\text{H}_5$; $R_4 = p\text{-BrC}_6\text{H}_4$.

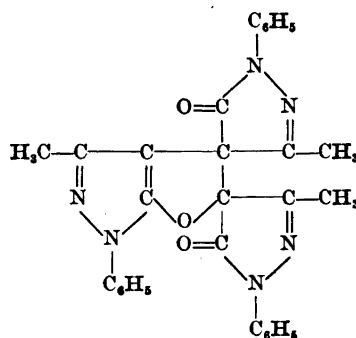


III

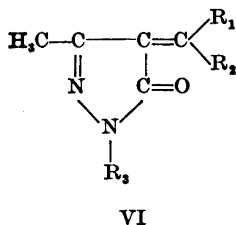


IV

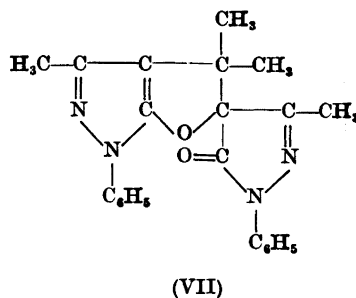
- a. $R = -\text{C} \begin{matrix} \text{CH}_2 \\ \text{CH}_2 \\ \text{CH}_3 \end{matrix}$
 b. $R = -\text{C} \begin{matrix} \text{CH}_2 \\ \text{CH}_2 \\ \text{C}_2\text{H}_5 \end{matrix}$
 c. $R = -\text{C} \begin{matrix} \text{Cl} \\ \text{CH}_3 \\ \text{CH}_2 \end{matrix}$
 (d. $R = -\text{C} \begin{matrix} \text{CH}_2 \\ \text{CHCH}_3 \end{matrix}$)



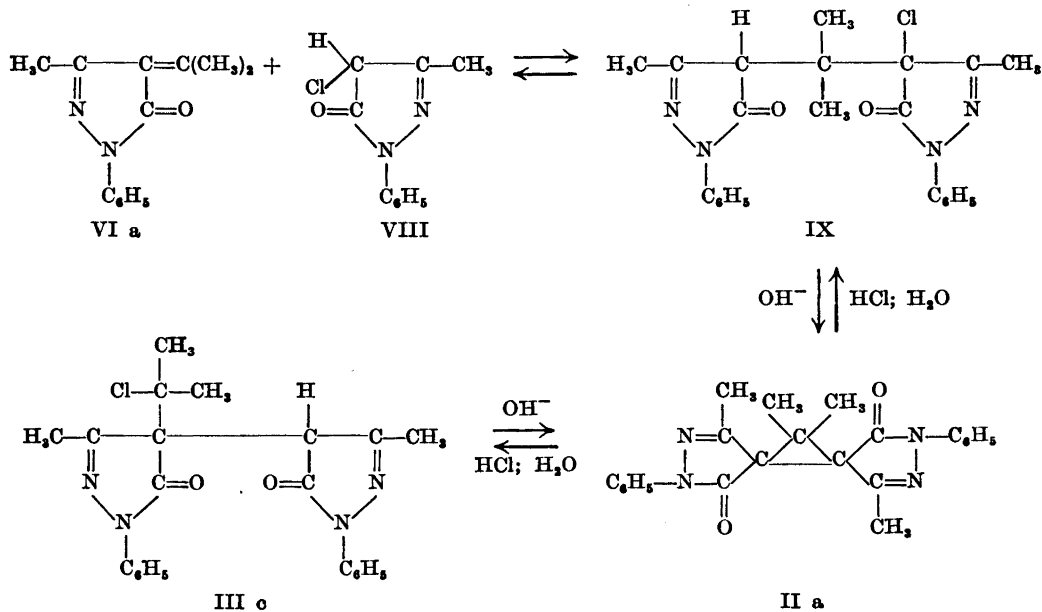
V



- a. $R_1 = R_2 = \text{CH}_3$; $R_3 = \text{C}_6\text{H}_5$.
 b. $R_1 = R_2 = \text{CH}_3$; $R_3 = p\text{-BrC}_6\text{H}_4$.
 c. $R_1 = \text{CH}_3$; $R_2 = \text{C}_2\text{H}_5$; $R_3 = \text{C}_6\text{H}_5$.



From the two possible structures of $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2$, II a and VII, VII may be excluded, for after addition of hydrogen chloride to a benzene solution of the product, 1,1'-diphenyl-3,3'-dimethyl-4-(1-chloro-1-methylethyl)-[4,4'-bi-2-pyrazoline]-5,5'-dione (III c) could be isolated in good yield. The dissociation products of 4-chloro-4,4'-isopropylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (IX), *viz.* VI a and VIII, were also formed. Dilute alkali splits off hydrogen chloride from III c, the main reaction being ring closure with reformation of II a (Scheme 1). Thus the structure of $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2$ is 2,8-diphenyl-4,10,11,11-tetramethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (II a). The formation of the *trans* isomer is most probable, but the existence of the *cis* isomer cannot be excluded.



Scheme 1.

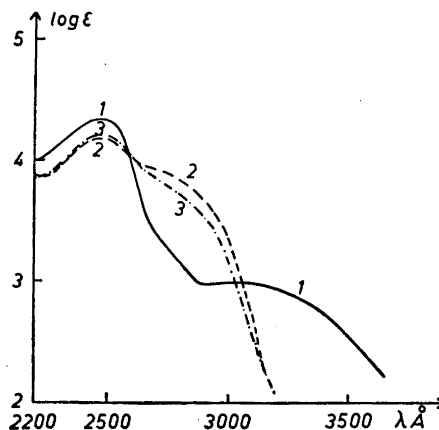


Fig. 1. UV absorption in ethanol of 1) II a, 2) III a, 3) III c.

A bromo derivative of II a, II c, has been prepared in two different ways a) by addition of the sodium salt of 1-*p*-bromophenyl-3-methyl-4-bromo-2-pyrazolin-5-one to 1-phenyl-3-methyl-4-*isopropylidene*-2-pyrazolin-5-one (VI a) and b) by addition of the sodium salt of 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one to 1-*p*-bromophenyl-3-methyl-4-*isopropylidene*-2-pyrazolin-5-one (VI b). The identity of the compounds obtained was demonstrated by UV and IR absorption measurements and affords another indication of the *cyclopropane* structure of II.

When boiled with ethanol for a few minutes or when left in acetone or alcohol solution at room temperature for some days, II a is quantitatively isomerized to a monobasic acid, for which the structure 1,1'-diphenyl-3,3'-dimethyl-4-*isopropenyl*-[4,4'-bi-2-pyrazoline]-5,5'-dione (III a) is proposed. The acid is stable towards hydrogen chloride and presents an UV absorption curve similar to the corresponding curve of 1,1'-diphenyl-3,3'-dimethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione². The existence of a $\text{CH}_2=\text{C}$ group in the acidic isomer was demonstrated by the method of Bricker and Roberts⁸.

A total of five derivatives of II a have been synthesized, *viz.* II b–f. Their UV absorption curves are almost identical with the curve of II a. According to various authors^{9–13} the IR spectra of *cyclopropane* derivatives contain a ring deformation band at 1 000–1 050 cm^{-1} . The spectra of II a–f show absorption at the long wave limit of this region. The steric arrangement of the groups in II b–f has not been investigated.

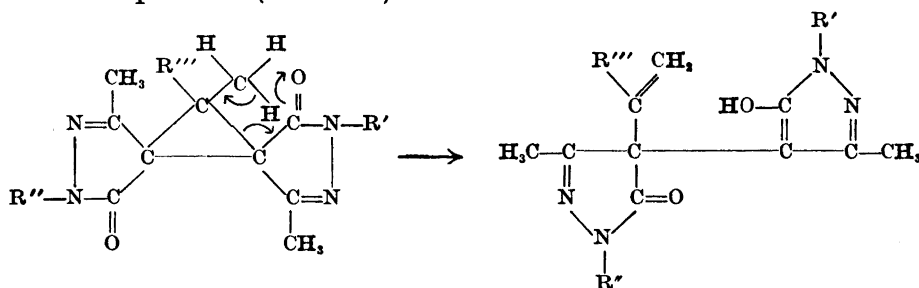
II b and c, like II a, when heated in dry state or in solution for a short time or when kept in solution at room temperature for some days, undergo ring cleavage with a hydrogen shift from one of the methyl groups attached to the *cyclopropane* ring to the 4 position of one of the pyrazolone rings. The *para* substituents do not appreciably affect the rate of isomerization. In acetone-ethanol solution (1:1, v/v) at 25° the monomolecular rate constants were found to be for II a 9.8×10^{-4} , for II b 9.6×10^{-4} and for II c 9.95×10^{-4} . In the case of II b and c two isomeric acids, e.g., 1-phenyl-1'-*p*-tolyl-3,3'-dimethyl-4-*isopropenyl*-[4,4'-bi-2-pyrazoline]-5,5'-dione and 1-phenyl-1'-*p*-tolyl-3,3'-di-

methyl-4'-isopropenyl-[4,4'-bi-2-pyrazoline]-5,5'-dione, can be formed. The rate constants indicate that about equal amounts of the two isomers are obtained. The mixtures have not been resolved.

2,8-Diphenyl-11-ethyl-4,10,11-trimethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione, II d, and its *p*-methyl and *p*-bromo derivatives, II e and f, isomerize with formation of acids under the same conditions as II a—c, though with greater ease. The monomolecular rate constants of the isomerization in acetone-ethanol solution (1:1, v/v) at 25° are for II d 1.36×10^{-3} , for II e 1.25×10^{-3} and for II f 1.35×10^{-3} .

For the isomerization product of II d there are two possible structures, III b and d. A test of end unsaturation⁸ was positive. A determination of the amount of C-methyl gave the same value as for III a. Accordingly 1,1'-diphenyl-3,3'-dimethyl-4-(1-ethylvinyl)-[4,4'-bi-2-pyrazoline]-5,5'-dione, III b, is the correct structure of the acid.

The isomerizations take place also in solvents like benzene which cannot supply protons for addition to the carbonyl groups. The acids formed during the reactions have no influence on the rates. An intramolecular rearrangement seems plausible (Scheme 2).



Scheme 2.

EXPERIMENTAL

1-*p*-Bromophenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one (VI b). This product was prepared in the same way as 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one (VI a) (Westö⁷). M.p. 155° (decomp.). (Found: C 53.3; H 4.5; Br 27.21; N 9.6; O 5.6. Calc. for $C_{13}H_{13}BrN_2O$: C 53.3; H 4.5; Br 27.26; N 9.6; O 5.5.)

2,8-Diphenyl-4,10,11,11-tetramethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (II a). 1-Phenyl-3-methyl-4-bromo-2-pyrazolin-5-one (2.16 g) was dissolved in an equivalent amount of N sodium hydroxide solution (7.2 ml) and ethanol (25 ml) at room temperature and immediately poured into a solution of 1.83 g of 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one (VI a) in ethanol (100 ml). Almost colourless crystals of II a separated. After 3–4 h the precipitate (2.32 g) was filtered, washed with ethanol and water and air-dried. The combined filtrate and washings were left overnight when another 0.51 g of II a separated. Both products were pure, yield 2.83 g. (Found: C 71.4; H 5.8; N 14.5; mol.wt. 379 (freezing point depression of benzene solutions). Calc. for $C_{22}H_{22}N_4O_2$: C 71.5; H 5.7; N 14.5; mol.wt. 386.) No sharp melting point was obtained because the compound isomerized into III a on heating. The solid product is stable at room temperature. For UV absorption curve, see Fig. 1.

2-*p*-Bromophenyl-8-phenyl-4,10,11,11-tetramethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (II c). a) 1-*p*-Bromophenyl-3-methyl-4-bromo-2-pyrazolin-5-one (crude product) was dissolved in ethanol (25 ml) and the equivalent amount of 2.5 N sodium hydroxide solution, and was then immediately poured into a solution of 1.81 g

of 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one (VI a) in ethanol (125 ml). After a few minutes II c started separating. When the separation was complete, the crystals were filtered and washed with ethanol and water, yield 4.42 g. (Found: C 59.2; H 4.55; Br 17.26; N 12.0; O 7.0. Calc. for $C_{23}H_{21}BrN_4O_2$: C 59.4; H 4.55; Br 17.17; N 12.0; O 6.9.)

b) II c was also prepared from 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one and 1-*p*-bromophenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one (VI b) in the same way as described above. Analyses, UV and IR absorption curves were identical for the product obtained here and the one obtained according to a).

2-Phenyl-8-*p*-tolyl-4,10,11,11-tetramethyl-2,3,8,9-tetrazadispiro [4.0.4.1]undeca-3,9-diene-1,7-dione (II b). 1-Phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one (8.32 g) was dissolved in ethanol (600 ml). Hydrobromide of 1-*p*-tolyl-3-methyl-4-bromo-2-pyrazolin-5-one (13.55 g of crude product) in ethanol (30 ml) was neutralized with 2.5 N sodium hydroxide solution using thymolphthalein as indicator and immediately poured into the above solution. The II b formed was filtered and washed with ethanol and water, yield 13.4 g, m.p. about 125° (decomp.). (Found: C 72.0; H 6.0; N 13.9. Calc. for $C_{24}H_{24}N_4O_2$: C 72.0; H 6.0; N 14.0.)

2,8-Diphenyl-11-ethyl-4,10,11-trimethyl-2,3,8,9-tetrazadispiro [4.0.4.1]undeca-3,9-diene-1,7-dione (II d). 1-Phenyl-3-methyl-4-bromo-2-pyrazolin-5-one (9.7 g) was dissolved in the equivalent amount of 1.63 N ethanolic piperidine (23.6 ml). The solution was immediately poured into a solution of 1-phenyl-3-methyl-4-*sec*-butylidene-2-pyrazolin-5-one (VI c) (10 g) in ethanol (125 ml). On scratching II d started separating. After 4 h the precipitate was filtered and washed with ethanol and water, yield 7.5 g. (Found: C 71.9; H 6.1; N 14.1. Calc. for $C_{24}H_{24}N_4O_2$: C 72.0; H 6.0; N 14.0.)

2-Phenyl-8-*p*-tolyl-11-ethyl-4,10,11-trimethyl-2,3,8,9-tetrazadispiro [4.0.4.1]undeca-3,9-diene-1,7-dione (II e) and 2-*p*-bromophenyl-8-phenyl-11-ethyl-4,10,11-trimethyl-2,3,8,9-tetrazadispiro [4.0.4.1]undeca-3,9-diene-1,7-dione (II f). II e and f were prepared analogously to II d from 1-phenyl-3-methyl-4-*sec*-butylidene-2-pyrazolin-5-one and 1-*p*-tolyl-3-methyl-4-bromo-2-pyrazolin-5-one or 1-*p*-bromophenyl-3-methyl-4-bromo-2-pyrazolin-5-one. (Found for II e: C 72.2; H 6.3; N 13.6. Calc. for $C_{25}H_{24}N_4O_2$: C 72.4; H 6.3; N 13.5. Found for II f: C 60.0; H 5.0; Br 16.65; N 11.7. Calc. for $C_{24}H_{23}BrN_4O_2$: C 60.1; H 4.8; Br 16.67; N 11.7.)

Addition of hydrogen chloride to $C_{23}H_{22}N_4O_2$ (neutral isomer). A solution of $C_{23}H_{22}N_4O_2$ in benzene was cooled in ice, and dry hydrogen chloride was passed into the solution for 15 min. After removal of the benzene under reduced pressure, the residue was dissolved in ethanol and precipitated with water, filtered, washed with water and air-dried. A yellow product was obtained.

When sodium acetate solution and a small amount of cupric sulphate were added to the filtrate, pyrazole blue precipitated, indicating the presence of 1-phenyl-3-methyl-4-chloro-2-pyrazolin-5-one.

With light petroleum at room temperature 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one could be extracted from the yellow, solid mixture. After recrystallization from ethanol, it melted at 116° alone and mixed with authentic 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one.

It is evident that a hydrochloride of 4-chloro-4,4'-isopropylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] is primarily formed from part of the $C_{23}H_{22}N_4O_2$, and that it is decomposed into hydrogen chloride, 1-phenyl-3-methyl-4-chloro-2-pyrazolin-5-one and 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one on addition of ethanol and water. As this chlorobispyrazolone is a minor part of the addition product, VII can not be the structure of $C_{23}H_{22}N_4O_2$. (According to light absorption measurements the mixture obtained contained about 20 % of 1-phenyl-3-methyl-4-isopropylidene-2-pyrazolin-5-one, corresponding to about 35 % cleavage of the C_6-C_6 bond of II a).

The main addition compound, which was not extracted by the light petroleum, was an almost colourless, acidic product. For UV curve see Fig. 1. (Found: C 65.3; H 5.6; Cl 8.29; N 13.15. Calc. for $C_{23}H_{23}ClN_4O_2$: C 65.3; H 5.5; Cl 8.38; N 13.25.) On addition of dilute alkali, the product split off hydrogen chloride with formation of the original 3-ring in about 75 % yield. The acidity of the addition product, its slight solubility in light petroleum and easy ring closure together with the lack of oxidative power (cf. Westöb¹⁴) show that the product is 1,1'-diphenyl-3,3'-dimethyl-4-(1-chloro-1-methylethyl)-[4,4'-bi-2-pyrazoline]-5,5'-dione (III c).

Isomerization of II a into 1,1'-diphenyl-3,3'-dimethyl-4-isopropenyl-[4,4'-bi-2-pyrazoline]-5,5'-dione (III a). II a (1.35 g) was boiled in ethanol (30 ml) until about 15 ml remained (30 min). On cooling colourless crystals separated (1.20 g). They were filtered, washed with cold ethanol and air-dried, m.p. 201° (decomp.). (Found: C 71.5; H 5.7; N 14.6; O 8.3; equiv.wt. 384. Calc. for $C_{23}H_{22}N_4O_2$: C 71.5; H 5.7; N 14.5; O 8.3; equiv.wt. 386). The existence of $CH_2=$ in the molecule was demonstrated by the method of Bricker and Roberts⁸, though only qualitatively. A quantitative determination did not succeed. For UV absorption curve, see Fig. 1.

When a weighed amount of II a was boiled in excess of ethanol for 5 min, cooled and titrated with barium hydroxide solution using thymolphthalein as indicator, the consumption of base corresponded to a quantitative isomerization into 1,1'-diphenyl-3,3'-dimethyl-4-isopropenyl-[4,4'-bi-2-pyrazoline]-5,5'-dione (III a). The same isomerization took place in a couple of days at room temperature in acetone or acetone-ethanol solution. Heating of solid II a at 140° for one hour also gave III a together with degradation products.

1,1'-Diphenyl-3,3'-dimethyl-4-isopropenyl-4'-bromo-[4,4'-bi-2-pyrazoline]-5,5'-dione. Because the mol.wt. of III a could not be determined on account of the slight solubility in benzene and glacial acetic acid of the product, the 4-bromo derivative was prepared for mol.wt. determination.

III a (0.80 g) was dissolved in acetic acid. A few pieces of ice were added, and bromine (0.34 g) in acetic acid was dropped into the solution. More ice and water precipitated the reaction product, which was filtered, washed with water and air-dried. The 4-bromobispyrazolone was isolated by solution of the mixture obtained in acetic acid and dropwise addition of water until yellow crystals started separating. The solution was then cooled in ice and the crystals formed were filtered and washed with dilute acetic acid and water. The product could be recrystallized from acetic acid. (Found: C 59.1; H 4.6; Br 17.3; N 11.9; mol.wt. 455. Calc. for $C_{23}H_{21}BrN_4O_2$: C 59.35; H 4.6; Br 17.2; N 12.0; mol.wt. 465.)

Isomerization of II d to form 1,1'-diphenyl-3,3'-dimethyl-4-(1-ethylvinyl)-[4,4'-bi-2-pyrazoline]-5,5'-dione (III b). II d (1.18 g) was refluxed in ethanol (10 ml) for 15 min. On cooling and scratching colourless crystals separated (0.92 g), m.p. 188° (decomp.). (Found: C 72.0; H 6.0; N 14.0; equiv.wt. 400. Calc. for $C_{24}H_{24}N_4O_2$: C 72.0; H 6.0; N 14.0; equiv.wt. 400.)

For the acid formed there are two possible structures, III b and d. A qualitative test of end unsaturation according to Bricker and Roberts⁸ was positive, thus supporting the formula III b. Furthermore, a determination of C-methyl on this product and on III a gave in both cases 10.1%. III a requires 11.7%, III b 11.3% and III d 15.0%. Accordingly III b must be the structure of the acid.

Isomerization of II b, c, e and f. The mono-*p*-methyl and mono-*p*-bromo derivatives, II b, c, e and f, could be isomerized by boiling them in ethanol or by keeping their solutions in acetone or acetone-ethanol at room temperature for some days. Two isomeric acids can be formed in each case, e.g., from II c 1-phenyl-1'-*p*-bromophenyl-3,3'-dimethyl-4-isopropenyl-[4,4'-bi-2-pyrazoline]-5,5'-dione and 1-phenyl-1'-*p*-bromophenyl-3,3'-dimethyl-4'-isopropenyl-[4,4'-bi-2-pyrazoline]-5,5'-dione. They have not been separated.

Reaction rates of the isomerizations. About 2 g of the cyclopropane derivatives were dissolved in 250 ml of acetone (25 ml) and so much commercial, anhydrous ethanol (warmed to 39° to compensate the decrease of temperature when the solvents are mixed) was added that the total volumes were 500 ml at 25.0°. The solutions were placed in a thermostat at $25.00^\circ \pm 0.05^\circ$. At intervals samples of 50.0 ml were titrated with barium hydroxide solution using thymolphthalein as indicator. The constants were calculated from the moment when the first sample was titrated.

The analyses were performed by the Department of Analytical Chemistry, University of Lund, or by Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim, Germany.

The financial support of *Statens naturvetenskapliga forskningsråd* is gratefully acknowledged.

REFERENCES

1. Westöö, G. *Acta Chem. Scand.* **7** (1953) 360.
2. Westöö, G. *Acta Chem. Scand.* **7** (1953) 352.
3. Cloke, J. B., Stehr, E., Steadman, T. R. and Westcott, L. C. *J. Am. Chem. Soc.* **67** (1945) 1587.

4. Radulescu, D. and Georgescu, V. *Bull. soc. chim. France* [4] **37** (1925) 187.
5. Prelog, V., Bauer, W., Cookson, G. H. and Westöö, G. *Helv. Chim. Acta* **34** (1951) 736.
6. Westöö, G. *Acta Chem. Scand.* **7** (1953) 355.
7. Westöö, G. *Acta Chem. Scand.* **11** (1957) 1285.
8. Bricker, C. E. and Roberts, K. H. *Anal. Chem.* **21** (1949) 1331.
9. Derfer, J. M., Pickett, E. E. and Boord, C. E. *J. Am. Chem. Soc.* **71** (1949) 2482.
10. Slabey, V. A. *J. Am. Chem. Soc.* **76** (1954) 3604.
11. Wiberley, S. E. and Bunce, S. C. *Anal. Chem.* **24** (1952) 623.
12. Bridson-Jones, F. S., Buckley, G. D., Cross, L. H. and Driver, A. P. *J. Chem. Soc.* **1951** 2999.
13. Bridson-Jones, F. S. and Buckley, G. D. *J. Chem. Soc.* **1951** 3009.
14. Westöö, G. *Acta Chem. Skand.* **6** (1952) 1499.

Received April 15, 1957.