ACTA CHEMICA SCANDINAVICA 11 (1957) 1359—1364

Studies on *Cyclo*propanes

II. Preparation and Properties of Some Penta- and Tetrasubstituted *Cyclo*propanes

GUNNEL WESTÖÖ

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

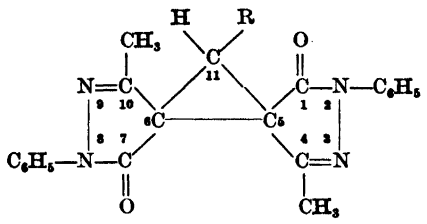
The pentasubstituted *cyclo*propanes, I b—e, and the tetrasubstituted one, I a, have been prepared. They are more stable towards isomerization than the hexasubstituted *cyclo*propane derivatives described in a previous paper [1]. On heating I a and I e are transformed into III a and III b.

2,8,11-Triphenyl-4,10-dimethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione, I e, could be prepared from 1-phenyl-3-methyl-4-benzylidene-2-pyrazolin-5-one and 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one analogously to the hexasubstituted products [1]. For the preparation of I a—d the corresponding 4,4′-alkylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-ones] [2] (II a—d) were used as starting materials. When their sodium salts were brominated or iodinated to form II h or II i, ring closure took place immediately at room temperature, I a—d precipitating in good yields (>90 %). The bromination was performed with a bromopyrazolone, *e.g.*, 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one or preferably 1-phenyl-3-methyl-4,4-dibromo-2-pyrazolin-5-one [3].

Analogous ring closures have been made with alkylidenebis[indanedione] and 2,2′-methylenebis[5,5-dimethyl-1,3-*cyclo*hexanedione] by Radulescu and Georgescu [4] and with methyl β-phenyl-γ-bromo-γ-benzoyl-ethylmalonate by Kohler and Conant [5].

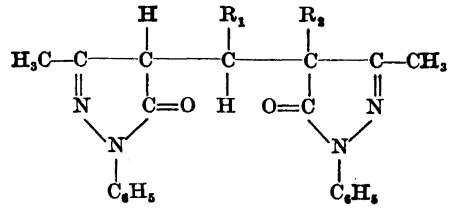
Good support for the *cyclo*propane structure of the reaction products is afforded by the UV curves (Fig. 1), which are almost identical with the corresponding curves of the hexasubstituted *cyclo*propanes described earlier [1]. The IR spectra [1,6,7] show absorption at 1 000—1 010 cm^{-1}. — The steric arrangement of the groups in I a—e has not been studied.

Hydrogen chloride adds to the compounds I a, b or c with formation of 4-chloro-4,4′-alkylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-ones], II e, f or g, as proved by the following facts. The products obtained are acids which in



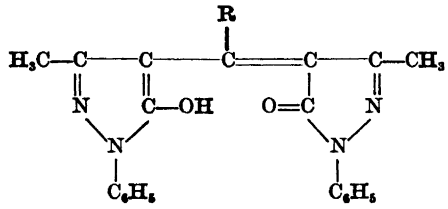
I

a. R = H.
b. R = CH_3.
c. R = C_2H_5.
d. R = *i*-C_3H_7.
e. R = C_6H_5.



II

a. R_1 = R_2 = H.
b. R_1 = CH_3; R_2 = H.
c. R_1 = C_2H_5; R_2 = H.
d. R_1 = *i*-C_3H_7; R_2 = H.
e. R_1 = H; R_2 = Cl.
f. R_1 = CH_3; R_2 = Cl.
g. R_1 = C_2H_5; R_2 = Cl.
h. R_1 = H or alkyl; R_2 = Br.
i. R_1 = H or alkyl; R_2 = I.



III

a. R = H.
b. R = C_6H_5.
(c. R = alkyl.)

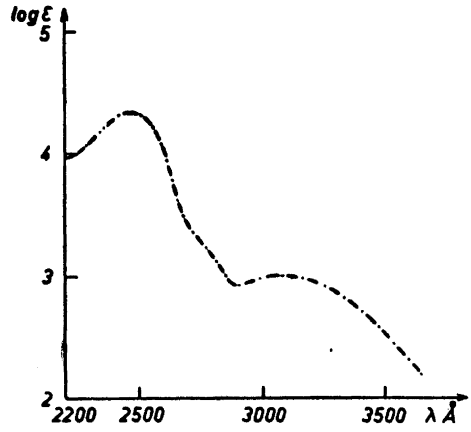


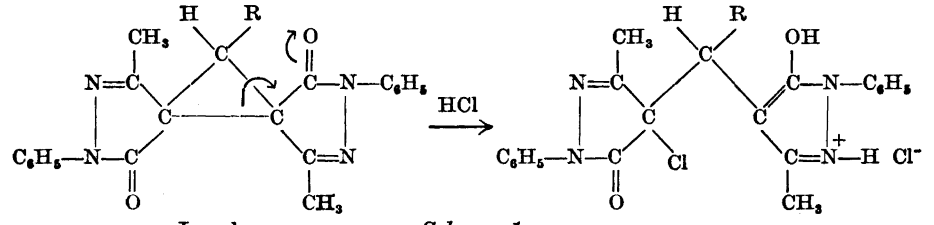
Fig. 1. UV curve of I b in ethanol.

acetate-buffered solution split off hydrogen chloride with reformation of I a, b or c. They oxidize iodides almost quantitatively to iodine at room temperature according to the equation (*cf.* Westöö [8]):

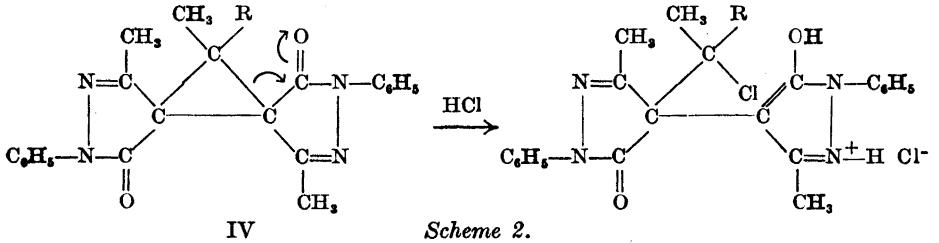
$$PyClCHRPyH\,{}^{*}+2KI \rightarrow PyHCHRPyK+I_2+KCl.$$

Contrary to 4-chloro-4,4′-*iso*propylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] [1] and 1,1′,1″-triphenyl-3,3′,3″-trimethyl-4-bromo-[4,4′,4″-ter-2-pyrazoline]-5,5′,5″-trione [9], II e, f and g do not dissociate into 1-phenyl-3-methyl-4-halogeno-2-pyrazolin-5-one and an α,β-unsaturated carbonyl compound.

The opening of the *cyclo*propane ring by hydrogen chloride is probably started by the addition of a proton to a carbonyl group, followed by an electron transfer from a *cyclo*propane bond to the pyrazolone ring and the uptake of a chloride ion by the most positive carbon atom. When C_{11} carries one methyl or ethyl group only, it is too electron-deficient to allow a displacement of the $C_5—C_{11}$ bonding electrons to the pyrazolone, and the $C_5—C_6$ bond breaks exclusively (Scheme 1). However, when C_{11} has two electron-releasing groups, a cleavage of the $C_5—C_{11}$ bond is instead the main reaction [1] (Scheme 2). Under the conditions described in the experimental part only about 20 % of the $C_5—C_6$ bonds were cleaved in the 11,11-dimethyl compound (IV a), 5 % in the 11-ethyl-11-methyl compound (IV b) in accordance with the increased inductive effect on C_{11}.



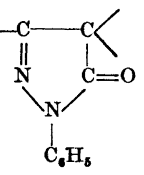
I a, b, c *Scheme 1*



IV *Scheme 2.*

a. R = CH_3.
b. R = C_2H_5.

* Py represents the group



The quantitative rearrangement, which was found in solution even at room temperature with the hexasubstituted *cyclo*propanes (cleavage of the *cyclo*propane ring with migration of a hydrogen atom from an 11-methyl group), has no analogue with the pentasubstituted products I b—d. These are quite stable at room temperature and are markedly more resistant towards heat than are the hexasubstituted ones. On prolonged heating of I b or c in dioxan-water at 95°, amorphous products were obtained. Besides degradation products the isomer Py = C(CH_2R)PyH has probably been formed, but it has not been isolated. I d is even more stable than I b and c and could be recovered to 90 % after heating at 95° for 24 h in dioxan-water solution.

Heating in solid form or in solution of the phenyl compound, I e, yielded 4,4'-benzylidynebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (III b)[10]. The same form of isomerization was found with the tetrasubstituted product I a, methylidynebis[1-phenyl-3-methyl-2-pyrazolin-5-one][11] (III a) being formed.

EXPERIMENTAL

2,8-Diphenyl-4,10-dimethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (I a). 4,4'-Methylenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II a) (2.5 g of crude product, obtained from the reaction of 1-phenyl-3-methyl-2-pyrazolin-5-one in benzene solution with formaldehyde at room temperature) was dissolved in ethanol (50 ml) and poured into a neutralized solution of 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one (1.5 g) in ethanol (15 ml). I a (2.0 g) separated immediately. It was collected by filtration and washed with ethanol and water. M.p. after crystallization from ethanol 162° (decomp.). (Found: C 70.5; H 5.0; N 15.7; mol.wt. 350 *. Calc. for $C_{21}H_{18}N_4O_2$: C 70.4; H 5.1; N 15.6; mol.wt. 358.)

2,8-Diphenyl-4,10,11-trimethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (I b). a) 4,4'-Ethylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one][3] (II b) (1.53 g) in ethanol (5 ml) was neutralized with 2.5 N sodium hydroxide solution using phenolphthalein as indicator. Excess of 1-phenyl-3-methyl-4,4-dibromo-2-pyrazolin-5-one (1.36 g) dissolved in ethanol (20 ml) was added. I b separated at once as a soft mass which on scratching was transformed into crystals. The product was filtered, washed with ethanol, dilute sodium hydroxide solution and water. Yield: 1.40 g of crude product, m.p. 130—131° (decomp.). After one crystallization from ethanol it melted at 131—132° (decomp.). (Found: C 71.0; H 5.4; N 15.1; mol.wt. 370 *. Calc. for $C_{22}H_{20}N_4O_2$: C 70.95; H 5.4; N 15.05; mol.wt. 372.) b) 4,4'-Ethylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II b) (2.60 g) was dissolved in ethanolic sodium hydroxide solution (10 ml of ethanol + 5.65 ml of 2.46 N aqueous NaOH solution). Iodine (1.76 g) dissolved in ethanol (25 ml) was added with stirring. Crystals of I b separated. They were filtered and washed with 50 % ethanol. Yield: 2.35 g, m.p. of crude product 131° (decomp.).

2,8-Diphenyl-4,10-dimethyl-11-ethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (I c) and 2,8-diphenyl-4,10-dimethyl-11-isopropyl-2,3,8,9-tetrazadispiro[4.0.4.1]-undeca-3,9-diene-1,7-dione (I d). These compounds were prepared from equimolar amounts of the sodium salts of the corresponding alkylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one][3] (II c and d) and 1-phenyl-3-methyl-4,4-dibromo-2-pyrazolin-5-one or iodine in the way described for I b. The yields were 90—95 % of the theoretical amounts. The m.p. of I c was 110° and of I d 163—164° (decomp.). (Found for I c: C 71.4; H 5.7; N 14.6. Calc. for $C_{23}H_{22}N_4O_2$: C 71.5; H 5.7; N 14.5. Found for I d: C 71.6; H 6.0; N 13.9. Calc. for $C_{24}H_{24}N_4O_2$: C 72.0; H 6.0; N 14.0.)

2,8,11-Triphenyl-4,10-dimethyl-2,3,8,9-tetrazadispiro[4.0.4.1] undeca-3,9-diene-1,7-dione (I e). 1-Phenyl-3-methyl-4-benzylidene-2-pyrazolin-5-one[12] (1.93 g) was dissolved in ether (80 ml) and ethanol (40 ml) and mixed with a neutralized solution (phenolphthalein) of 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one (1.87 g) in ethanol (40 ml). When the

* determined by measurements of the freezing-point depressions of benzene solutions.

mixture had been decolorized, the ether was evaporated under reduced pressure. The precipitate was filtered and washed with ethanol and water. Yield: 3.10 g, m.p. 132°. (Found: C 74.5; H 5.1; N 12.8. Calc. for $C_{27}H_{22}N_4O_2$: C 74.6; H 5.1; N 12.9.)

Cleavage of the cyclopropane ring of I c with hydrogen chloride. I c (0.55 g) was dissolved in benzene, and dry hydrogen chloride was introduced with ice-cooling until the solution was saturated. After one hour the solvent was removed under reduced pressure; the solid residue was dissolved in ethanol, precipitated with water, filtered and washed with water. Yield: 0.48 g. (Found: C 65.0; H 5.5; Cl 8.5; N 13.0. Calc. for $C_{23}H_{23}ClN_4O_2$: C 65.3; H 5.5; Cl 8.4; N 13.25.)

When a buffered ethanol solution (50 ml of 1.8 N aqueous sodium acetate solution + ethanol to 500 ml) of the acid obtained was left for a few hours, hydrogen chloride was split off, and the three-ring was reformed quantitatively, as could be shown by UV measurement.

The chloro compound oxidized hydrogen iodide to iodine rapidly at room temperature.

0.0984 g of the addition product was dissolved in ethanol (10 ml) and mixed with an excess of potassium iodide dissolved in water (3 ml). After 3 min 5 N hydrochloric acid (3 ml) was added and the solution was titrated with 0.0998 N sodium thiosulphate solution. 4.65 ml was consumed. This corresponds to pure $PyClCH(C_2H_5)PyH$, II g. Another sample gave 97 % of $PyClCH(C_2H_5)PyH$.

Cleavage of the cyclopropane ring of I b with hydrogen chloride. I b (1.00 g) was dissolved in benzene (10 ml). Dry hydrogen chloride was introduced for 15 min into the ice-cooled solution, which was then kept in the ice bath for 2 h. The benzene was evaporated under reduced pressure, the solid residue was dissolved in ethanol (25 ml) and the solution was poured into water (200 ml) with stirring. The precipitate formed (II f) was filtered and washed with water. Yield: 1.02 g of almost colourless acid. It was purified by solution in ether and precipitation with light petroleum. (Found: C 64.5; H 5.3; Cl 8.6; N 13.6; O 7.7. Calc. for $C_{22}H_{21}ClN_4O_2$: C 64.6; H 5.2; Cl 8.7; N 13.7; O 7.8.)

Ring closure and oxidation of iodide were performed as for II g and with the same results.

Cleavage of I a by hydrogen chloride. I a was cleaved with hydrogen chloride in the same way as described for I b and c, II e being the main product formed. (Found: C 63.7; H 5.0; Cl 9.0; N 14.1; O 8.2. Calc. for $C_{21}H_{19}ClN_4O_2$: C 63.9; H 4.85; Cl 9.0; N 14.2; O 8.1.)

The addition product oxidized hydrogen iodide to iodine in about 90 % yield according to the procedure described for II g (time of reaction 1 min instead of 3). The low iodine yield may be caused by some hydrogen iodide splitting off from $PyICH_2PyH$.

When an ethanol solution of the product was titrated with barium hydroxide solution, I a (identified by its m.p. 162° (decomp.), UV curve and neutrality) separated during the titration. In acetate-buffered solution ring closure also took place as could be shown by UV measurements. When a concentrated ethanol solution of the addition product was left for some weeks, methylidynebis[1-phenyl-3-methyl-2-pyrazolin 5-one][11] (III a) separated, m.p. alone and mixed with an authentic sample 182.5°.

Cleavage of 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 (IV b) by hydrogen chloride [1]. IV b (0.25 g) was dissolved in ice-cooled benzene [20 ml) saturated with hydrogen chloride. After 15 min the solvent was removed under reduced pressure, the residue was dissolved in ethanol (5 ml) and poured into water (50 ml) with stirring. The precipitate formed was filtered and washed with water. Yield: 0.25 g of faintly yellow product. According to light absorption measurements less than 3 % of 1-phenyl-3-methyl-4-*sec*-butylidene-2-pyrazolin-5-one was present in the mixture, indicating that the C_5-C_6 bond had been cleaved to about 5 %.

When 2,8-diphenyl-4,10,11,11-tetramethyl-2,3,8,9-tetrazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (IV a) was treated in the way described above, about 12 % of the reaction product was 1-phenyl-3-methyl-4-*iso*propylidene-2-pyrazolin-5-one.

Bromination of $C_{23}H_{23}ClN_4O$. The chloro compound II g (0.19 g) was dissolved in acetic acid, and the equimolar amount of bromine (0.07 g) in acetic acid and a few pieces of ice were added. The product formed was precipitated with more ice and water, filtered, washed with water and air-dried. Yield: 0.22 g of yellow crystals, m.p. 123° (decomp.). Recrystallization from ethanol did not change the m.p. (Found: C 55.2; H 4.5; Br 16.1; Cl 7.2. Calc. for $C_{23}H_{22}BrClN_4O_2$: C 55.0; H 4.4; Br 15.9; Cl 7.1.)

Isomerization of I e to form 4,4'-benzylidynebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (III b). I e was heated in an oil bath at 135° for two hours or in dioxan-water (10:1)

solution at 95° for 20 h. Recrystallization from ethanol gave orange crystals, which melted at 240–241.5° (decomp.). Michaelis and Zilg [10] give m.p. 242° for III b. (Found: C 74.8; H 5.1; N 12.9. Calc. for $C_{27}H_{22}N_4O_2$: C 74.6; H 5.1; N 12.9.)

Isomerization of I a to form 4,4'-methylidynebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (III a). I a (0.50 g) in ethanol (30 ml) was refluxed for 24 h. On cooling orange crystals (0.43 g) separated. After crystallization from ethanol they melted at 183°. According to Ionescu and Georgescu [11] III a melts at 180°. (Found: C 70.1; H 5.2; N 15.6; equiv.wt. 354. Calc. for $C_{21}H_{18}N_4O_2$: C 70.4; H 5.1; N 15.6; equiv.wt. 358.)

Attempts to isomerize I b, I c, and I d. Boiling of I b or I c in ethanol solution overnight was not sufficient to decompose the *cyclo*propane rings completely. More than 25 % of unaltered I b or c could be isolated from the orange-red products.

Heating at 95° in dioxan-water (10:1, v:v) for 24 h destroyed the three-rings of I b and c. However, when I d was heated in the same way, about 90 % of the starting material could be recovered unchanged.

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

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

REFERENCES

1. Westöö, G. *Acta Chem. Scand.* **11** (1957) 1290.
2. Westöö, G. *Acta Chem. Scand.* **11** (1957) 1285.
3. Westöö, G. *Acta Chem. Scand.* **7** (1953) 456.
4. Radulescu, D. and Georgescu, V. *Bull. soc. chim. France* [4] **37** (1925) 187.
5. Kohler, E. P. and Conant, J. B. *J. Am. Chem. Soc.* **39** (1917) 1404.
6. Derfer, J. M., Pickett, E. E., and Boord, C. E. *J. Am. Chem. Soc.* **71** (1949) 2482.
7. Slabey, V. A. *J. Am. Chem. Soc.* **76** (1954) 3604.
8. Westöö, G. *Acta Chem. Scand.* **6** (1952) 1499.
9. Westöö, G. *Acta Chem. Scand.* **7** (1953) 355.
10. Michaelis, A. and Zilg, A. *Ber.* **39** (1906) 370.
11. Ionescu, M. V. and Georgescu, V. N. *Bull. soc. chim. France* [4] **41** (1927) 881.
12. Knorr, L. *Ann.* **238** (1887) 137.

Received May 23, 1957.