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Studies on *Cyclo*propanes

III. On the Isomerization of Certain Hexasubstituted *Cyclo*propanes

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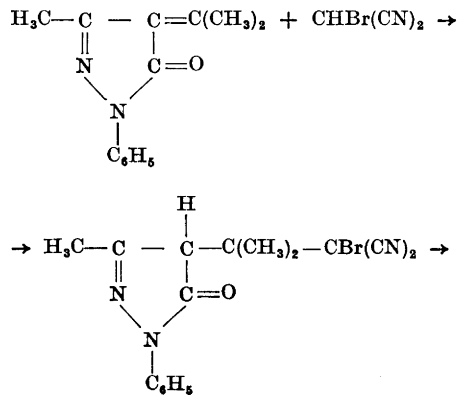
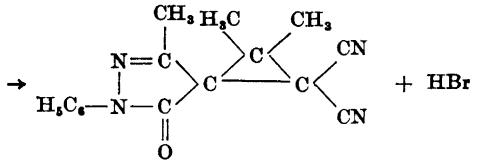
The rearrangement of certain hexasubstituted *cyclo*propanes, involving cleavage of the *cyclo*propane ring with migration of a hydrogen atom from a methyl group attached to the ring, which was described in a previous paper [1], has been further studied. I a and b isomerize at elevated temperatures, IV a, b being formed. Boiling with acids or bases transforms IV a, b into V. II rearranges easily with formation of VI and VII, but no rearrangement was observed with the compounds III a–e.

The hexasubstituted, neutral *cyclo*propanes (I—III), the isomerizations of which are studied in the present investigation, all have four electrophilic groups (1,1- and 2,2-positions) and — except for III e — two alkyl groups, one of which is a methyl, attached to the *cyclo*propane ring. With the exception of III a, b and e, they have all been prepared by a Michael addition of a bromo compound to an α,β-unsaturated carbonyl compound, followed by ring closure with expulsion of hydrogen bromide, *e. g.*





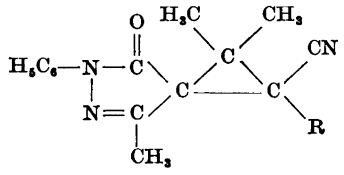
Alkali has been used to catalyse the reactions.

III a has been prepared by Ramberg and Wideqvist [2] and III b by Wideqvist [3], and their method of preparation could be used also for III e.

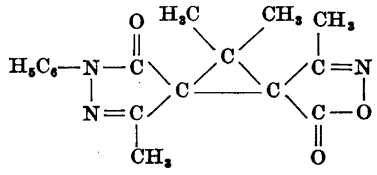
I a and I b are both stable at room temperature even in alcoholic solution and much more resistant towards heat than were the *cyclo*propanes, described in Studies on *Cyclo*propanes I [1]. However, heating in *n*-butanol on a boiling-water bath for several hours causes rearrangement to monobasic acids, which must have the structures IV a and IV b, on account of the fact that heating with concentrated hydrochloric acid or dilute alkali solution transforms them into a monobasic acid of the structure V. A qualitative test of end unsaturation according to Bricker and Roberts [4] was distinctly positive for IV but doubtable for V. This indicates a rearrangement of V from the β,γ-unsaturated nitrile structure to the α,β-form. The IR-spectrum of V presents a nitrile stretching band at 2 200 cm^{-1}, showing that the CN group is in strong resonance [5] (α,β-form). V exhibits a remarkable stability towards hydrolysis, a fact which also supports the α,β-unsaturated structure.

The compound II is less stable than I, and rearranges on boiling in ethanol solution for half an hour. The two possible isomerization products, the acids VI and VII, are both formed. They can be separated by recrystallization from ethanol. The isomer that is least soluble in ethanol is similar to IV in being rather soluble in concentrated hydrochloric acid, indicating that it has a pyrazolonyl group in the end position (VI), enabling the formation of NH tautomer. The other isomer (VII) is insoluble in concentrated hydrochloric acid. The UV spectra support these structures. In VI as well as in VII the main absorbing group in the UV range is the pyrazolonyl group. This group can form salts with acids in VI but not in VII. In accordance with this fact, the UV curve of VII is only slightly affected by strong acids, whereas the absorption of VI is appreciably depressed at wavelengths >250 mμ.

The compounds III a—d are all stable and do not isomerize even on prolonged boiling in ethanol or *n*-butanol. III e decomposes when boiled in *n*-butanol. No isomerization products could be isolated.



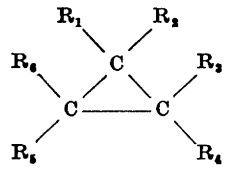
I



II

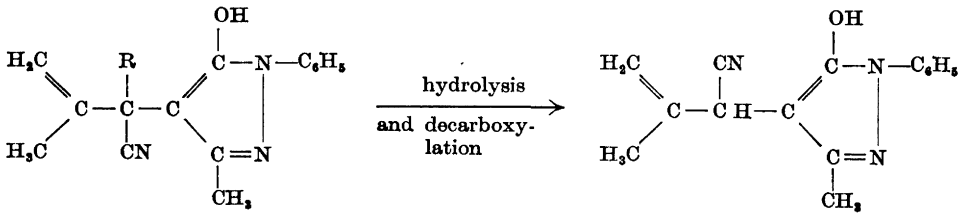
a. R=CN

b. R=$CONH_2$



III

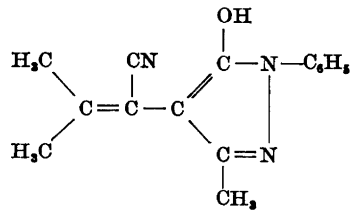
a. $R_1=R_2=CH_3$; $R_3=R_4=R_5=R_6=CN$
b. $R_1=CH_3$; $R_2=C_2H_5$; $R_3=R_4=R_5=R_6=CN$
c. $R_1=R_2=CH_3$; $R_3=R_4=R_5=CN$; $R_6=COOC_2H_5$
d. $R_1=CH_3$; $R_2=C_2H_5$; $R_3=R_4=R_5=CN$; $R_6=COOC_2H_5$
e. $R_1=CH_3$; $R_2=CH_3COCH_2CH_2$; $R_3=R_4=R_5=R_6=CN$



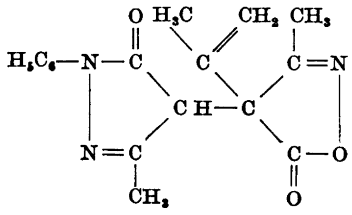
IV

a. R=CN
b. R=CONH$_2$

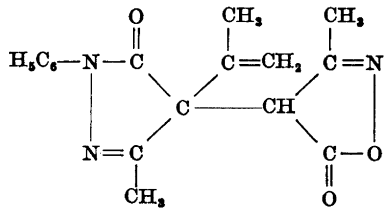
⇅



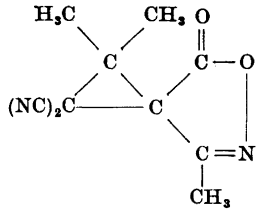
V



VI



VII



VIII

Unsuccessful attempts have been made also to prepare and study *cyclo*propanes with the substituents $R_1 = R_2 = CH_3$, $R_3 = CN$, $R_4 = CN$ or $COOC_2H_5$ and $R_5 = R_6 = COCH_3$. Acetone, sodium bromoacetylacetonate and malonitrile or ethyl cyanoacetate were used as starting material, but the reaction products isolated did not contain any component emanating from the acetone and were not *cyclo*propanes. From the nitrile and the bromoacetylacetone a furan derivative was obtained and from ethyl cyanoacetate and the bromoacetylacetone a substituted pyran. These products are described in a separate paper [6].

EXPERIMENTAL

Preparation of I a. 1-Phenyl-3-methyl-4-*iso*propylidene-2-pyrazolin-5-one (4.3 g) was dissolved in 250 ml of hot ethanol, the solution was immediately cooled to room temperature and bromomalonitrile (2.90 g) was added. As soon as it had dissolved, 2.39 N sodium hydroxide solution (8.4 ml) was added dropwise with stirring. The colourless I a soon started separating, and after 4 h it was collected by filtration and washed with 50 % ethanol. Yield: 4.5 g. The product was recrystallized from ethanol. M. p. 163° (decomp.). (Found: C 69.2; H 5.0; N 20.0. Calc. for $C_{16}H_{14}N_4O$: C 69.05; H 5.1; N 20.1.)

Preparation of I b. 1-Phenyl-3-methyl-4-*iso*propylidene-2-pyrazolin-5-one (4.3 g) and bromocyanoacetamide (3.3 g) were dissolved in 250 ml of ethanol. Sodium hydroxide (8.4 ml of 2.39 N solution) was added dropwise with stirring to the cold solution. The next day the colourless crystals which had separated were collected by filtration and washed with 50 % ethanol. Yield: 3.7 g; m. p. about 160° (very unsharp, decomp.). (Found: C 64.8; H 5.6; N 18.8; O 10.9. Calc. for $C_{16}H_{16}N_4O_2$: C 64.8; H 5.4; N 18.9; O 10.8.)

Preparation of II. 1-Phenyl-3-methyl-4-bromo-2-pyrazolin-5-one (5.07 g) was dissolved in ethanolic sodium hydroxide solution (10 ml of ethanol + 8.27 ml of 2.42 N aqueous sodium hydroxide solution) and immediately poured into a solution of 3-methyl-4-*iso*propylidene-2-isoxazolin-5-one [7] (2.78 g) in ethanol (75 ml). II separated at once. It was filtered and washed with water and ethanol. Yield of almost colourless product: 5.90 g, m. p. 160° (decomp.). The product was recrystallized by dissolving 1 g of it in 100 ml of boiling ethanol and immediate cooling of the solution in ice. (Found: C 65.4; H 5.4; N 13.5. Calc. for $C_{17}H_{17}N_3O_3$: C 65.6; H 5.5; N 13.5.)

The UV curve of II is closely related to the corresponding curves of the *cyclo*propane derivatives described in Studies on *Cyclo*propanes I [1]. The product is neutral towards thymolphthalein but is rapidly hydrolysed by alkali.

Preparation of III c. Ethyl *iso*propylidenecyanoacetate (3.06 g) and bromomalonitrile (2.90 g) were dissolved in ethanol (10 ml), and 8.55 ml of 2.34 N sodium hydroxide solution were added with stirring. III c started separating immediately, and after 3 h it was filtered and washed with 50 % ethanol. Yield: 3.3 g of colourless product; m. p. about 135° (decomp.). The product was purified by recrystallization from ethanol. (Found: C 60.8; H 5.2; N 19.35; O 14.7. Calc. for $C_{11}H_{11}N_3O_2$: C 60.8; H 5.1; N 19.35; O 14.7.)

Preparation of III d. Ethyl *sec.*-butylidenecyanoacetate (5.0 g of crude product) and bromomalonitrile (4.35 g) were dissolved in ethanol (20 ml). Sodium hydroxide (12.6 ml of 2.34 N solution) was added. III d separated in colourless crystals, and after 4 h it was filtered and washed with 50 % ethanol. Yield: 4.5 g; m. p. 89°. The product was purified by recrystallization from ethanol. M. p. 89.3°. (Found: C 62.3; H 5.7; N 18.1; O 13.7. Calc. for $C_{12}H_{13}N_3O_2$: C 62.3; H 5.7; N 18.2; O 13.8.)

Preparation of III e. 2,5-Hexanedione (1.14 g) and bromomalonitrile (2.90 g) were dissolved in ethanol (10 ml), and a solution of potassium iodide (7.0 g) in water (10 ml) was added. The following day the precipitate formed (III e) was filtered and washed with 50 % ethanol. Yield: 1.15 g. The compound was purified by recrystallization from ethanol, when a colourless, neutral product was obtained. M. p. 165—166° (decomp.). (Found: C 63.7; H 4.5; N 24.8; O 7.1. Calc. for $C_{12}H_{10}N_4O$: C 63.7; H 4.5; N 24.8; O 7.1.)

Isomerization of I a to form IV a. I a (3.0 g) was heated in 1-butanol (120 ml) on a boiling-water bath for 6—7 h. The butanol was evaporated under reduced pressure, and the crude IV a left was recrystallized repeatedly from ethanol. M. p. 163—164° (decomp.). (Found: C 69.2; H 5.1; N 20.0; O 5.6; equiv. wt 278. Calc. for $C_{16}H_{14}N_4O$: C 69.05; H 5.1; N 20.1; O 5.75; equiv. wt 278.) A CH_2=C determination according to Bricker and Roberts [4] was positive.

Boiling of IV a with a) concentrated hydrochloric acid or b) dilute sodium hydroxide solution to form V. a) IV a (1.35 g) was heated with concentrated hydrochloric acid (20 ml) on a water-bath for 3 h. The hydrochloric acid was removed under reduced pressure, and the solid residue was boiled with water. On cooling colourless crystals separated. They were filtered and washed with water. Yield: 1.03 g. After recrystallization from ethanol twice the product melted at 173° on slow heating. When the melting tube was inserted in the heating-block at ~130°, the product melted, but solidified again and then melted at ~173°. (Found: C 70.9; H 6.1; N 16.4; O 6.4; equiv. wt 252. Calc. for $C_{15}H_{15}N_3O$: C 71.1; H 6.0; N 16.6; O 6.3; equiv. wt 253.) A qualitative test on unsaturation according to Bricker and Roberts gave only weak colour. The product is not hydrolysed by concentrated hydrochloric acid, nor by 2 N sodium hydroxide solution at 100°.

b) A solution of IV a (0.2 g) in 2.4 N sodium hydroxide solution (2.5 ml) was heated on a water-bath for 8 h. On acidification V separated. It was collected by filtration and washed with water. From the solution more V could be extracted with ether. Mixed melting point with an authentic sample of V was 172°.

Isomerization of I b to form IV b. I b (2.0 g) and 1-butanol (60 ml) were heated in a boiling-water bath for 6 h. The butanol was evaporated under reduced pressure and the solid residue was recrystallized from ethanol. Yield: 1.6 g of colourless IV b; m. p. about 215° (decomp.). (Found: C 64.8; H 5.5; N 18.9; O 10.9; equiv. wt 296. Calc. for $C_{16}H_{16}N_4O_2$: C 64.85; H 5.4; N 18.9; O 10.8; equiv. wt 296.) A test on end unsaturation according to Bricker and Roberts was positive.

IV b, analogously to IV a, could be transformed into V by heating with concentrated hydrochloric acid on a boiling-water bath.

Isomerization of II to form VI and VII. A solution of II (5.05 g) in ethanol (500 ml) was boiled vigorously for half an hour. At that time so much solvent had evaporated that crystals of VI started separating. After cooling the product was collected by filtration and washed with cold ethanol. Yield of VI: 2.35 g. The compound can be recrystallized from ethanol. M. p. 187° (decomp.). (Found: C 65.6; H 5.5; N 13.5; O 15.2; equiv. wt 308. Calc. for $C_{17}H_{17}N_3O_3$: C 65.6; H 5.5; N 13.5; O 15.4; equiv. wt 311.) A qualitative test on CH_2=C according to Bricker and Roberts [4] was positive. The product is soluble in concentrated hydrochloric acid.

The mother liquor and washings from VI were evaporated to dryness in vacuum. The product obtained was recrystallized from ethanol, treated with concentrated hydrochloric acid to remove VI, filtered, washed with hydrochloric acid and water and once more recrystallized from ethanol. Yield of VII: 1.25 g, m. p. 179° (decomp.). (Found: C 65.5; H 5.7; N 13.5; O 15.5; equiv. wt 309. Calc. for $C_{17}H_{17}N_3O_3$: C 65.6; H 5.5; N 13.5; O 15.4; equiv. wt 311.) A qualitative test on end unsaturation was positive.

The UV curves of VI and VII are distinctly different (λ_{max_1} = 246 mμ, log ε_1 = 4.09 and λ_{max_2} = 275 mμ, log ε_2 = 3.98 for VI, λ_{max} = 248 mμ, log ε = 4.34 for VII).

Preparation of VIII. When bromomalonitrile (4.35 g) was dissolved in a solution of 3-methyl-4-*iso*propylidene-2-isoxazolin-5-one (4.17 g) in ethanol (150 ml), VIII started separating immediately. After 4 h it was filtered and washed with 50 % ethanol. Yield:

4.95 g of colourless product; m. p. ~173° (decomp.). The compound was recrystallized from ethanol. (Found: C 59.3; H 4.5; N 20.7. Calc. for $C_{10}H_9N_3O_3$: C 59.1; H 4.5; N 20.7.) The product is rapidly hydrolysed by alkali. A solution of the compound in concentrated acetic acid does not react with bromine at room temperature. Accordingly it does not contain the isomeric acid. The IR spectrum shows absorption at 1 025 cm^{-1}, which is within the range characteristic of *cyclo*propane rings [8,9].

Attempts to isomerize III a—e. Heating of ethanol or 1-butanol solutions of III a, b, c, d or e on a boiling-water bath did not result in rearrangements with ring cleavage. Except with III e most of the *cyclo*propane derivative could be recovered unchanged.

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