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Studies on Pyrazolones

XI. Reactions between 1-Phenyl-3-methyl-2-pyrazolin-5-one and Some Aliphatic Carbonyl Compounds

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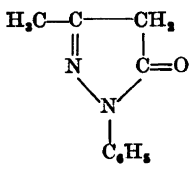
Aliphatic aldehydes and 1-phenyl-3-methyl-2-pyrazolin-5-one (I) react with the formation of 4,4′-alkylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-ones] (II a—e). No 1-phenyl-3-methyl-4-alkylidene-2-pyrazolin-5-ones (III a) could be isolated.

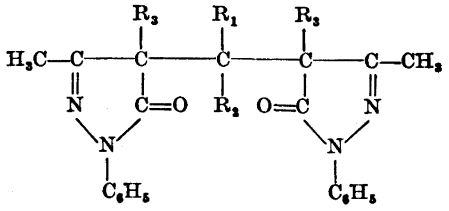
Methylalkyl ketones and I yield 1-phenyl-3-methyl-4-(1-methylalkylidene)-2-pyrazolin-5-ones (III b, c) and 4,4′-(1-methylalkylidene)-bis[1-phenyl-3-methyl-2-pyrazolin-5-ones] (II f, g). In solution II f and g — contrary to II a—e — are strongly dissociated into I and III (b, c).

1-Phenyl-3-methyl-2-pyrazolin-5-one (I) reacts rapidly at room temperature with aliphatic aldehydes, colourless, crystalline, stable acids, 4,4′-alkylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-ones] (II a—e) being formed. In anhydrous 1,2-diaminoethane they can be titrated as dibasic acids with sodium methoxide in benzene-methanol solution using *o*-nitroaniline as indicator [1,2], but under ordinary conditions — in ethanol - water using phenolphthalein as indicator — they are titrated as monobasic acids. They form 4,4′-dibromo compounds, *e.g.*, II h. Only one alkylidene compound, preparable from an aliphatic aldehyde and I, has been described in the literature before, *viz.* the methylene compound [3-5].

A comparison between the acidic properties of II a—e and 1,1′,1″-triphenyl-3,3′,3″-trimethyl-4,4′,4″-ter-[2-pyrazoline-5,5′,5″-trione] [IV][6] shows a great difference in the dissociability of the second 4-H atom, caused by the different electron affinity of the alkylidene and pyrazolonylidene groups, the electron donating alkylidene groups weakening the acidic strength, the electron attracting pyrazolonylidene group increasing the acidity remarkably. Thus IV is titrated as a dibasic acid in aqueous ethanol with barium hydroxide using phenolphthalein as indicator, whereas even on titration in dimethylformamide solution with sodium methoxide in benzene-methanol using azo violet as indicator [7], II a—e turn out as monobasic acids.

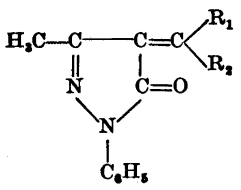


I



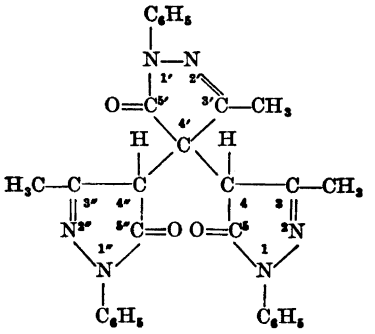
II

a. $R_1 = R_3 = H$; $R_2 = CH_3$.
b. $R_1 = R_3 = H$; $R_2 = C_2H_5$.
c. $R_1 = R_3 = H$; $R_2 = n\text{-}C_3H_7$.
d. $R_1 = R_3 = H$; $R_2 = i\text{-}C_3H_7$.
e. $R_1 = R_3 = H$; $R_2 = n\text{-}C_6H_{13}$.
f. $R_1 = R_2 = CH_3$; $R_3 = H$.
g. $R_1 = CH_3$; $R_2 = C_2H_5$; $R_3 = H$.
h. $R_1 = H$; $R_2 = CH_3$; $R_3 = Br$.



III

(a. $R_1 = H$; R_2 = alkyl.)
b. $R_1 = R_2 = CH_3$.
c. $R_1 = CH_3$; $R_2 = C_2H_5$.
(d. $R_1 = R_2 = C_2H_5$.)

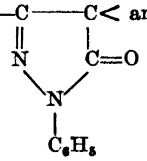


IV

From reactions between acetone and I Knorr [8], with excess of acetone, isolated 1-phenyl-3-methyl-4-*iso*propylidene-2-pyrazolin-5-one (III b) and, with equivalent amounts of reactants, an acid for which he proposed the structure 4,4′-*iso*propylidenebis [1-phenyl-3-methyl-2-pyrazolin-5-one] (II f), though without proof.

A closer investigation of the reaction showed that I rapidly adds to III b with formation of a bispyrazolone. Accordingly, even with great excess of acetone, bispyrazolone is formed in the beginning of the reaction when the concentration of I is large. However, there exists an equilibrium *

$$PyH_2 + Py{=}C(CH_3)_2 \rightleftharpoons PyHC(CH_3)_2PyH$$

* Py represents the group  and tautomeric forms.

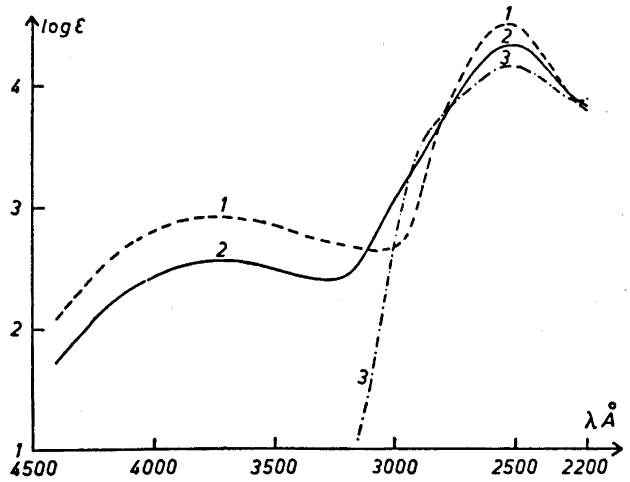


Fig. 1. UV absorption curves of 1) 1-phenyl-3-methyl-4-*iso*propylidene-2-pyrazolin-5-one (III b), 2) 4,4′-*iso*propylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II f) and 3) 4,4′-propylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II b), showing the stability of II b and the dissociation of II f.

and on prolonged boiling with acetone all pyrazolone is therefore transformed into III b.

The structure of the bispyrazolone is difficult to settle by direct study on account of its strong dissociation into I and III b in solution. But the analogy to the corresponding compounds (II a—e) obtained from aldehydes and the plausibility that a Michael addition takes place between I and III b are in favour of the structure II f. The equivalent weight of II f cannot be determined, for both I and III b consume alkali, III b probably mainly by addition of the ethanol used as solvent to form a salt of the unstable acid 1-phenyl-3-methyl-4-(1-ethoxy-1-methylethyl)-2-pyrazolin-5-one (*cf.* Westöö [9]).

Methylethylketone reacts with I analogously to acetone, 1-phenyl-3-methyl-4-*sec*-butylidene-2-pyrazolin-5-one (III c) and 4,4′-*sec*-butylidenebis-[1-phenyl-3-methyl-2-pyrazolin-5-one] (II g) being formed. III c is rather unstable at room temperature. The corresponding diethyl compound, III d, is still more unstable and could not be isolated from the reaction between diethylketone and I. Similar to II f, but contrary to II a—e, II g is strongly dissociated into I and III c in solution. The difference in stability between the alkylidene and 1-methylalkylidene compounds (see Fig. 1), may be caused by III a being less stabilized by hyperconjugation and presenting less hindrance towards addition than III b or c (steric and inductive effects).

EXPERIMENTAL

4,4'-Ethylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II a). Finely divided 1-phenyl-3-methyl-2-pyrazolin-5-one (I), recrystallized from ethyl acetate, (10 g) was dissolved in acetaldehyde (30 ml). On scratching colourless crystals separated. They were collected by filtration and washed with light petroleum. The product was purified by solution in benzene and precipitation with light petroleum, yield 9.3 g. After recrystallization from ethanol (solution in 15 ml at room temperature, crystallization on scratching, yield 8.4 g) it melted at 173° (decomp.). (Found: C 70.3; H 5.9; N 14.9; equiv. wt. 372 on titration in aqueous ethanol with barium hydroxide using phenolphthalein as indicator, 185 on titration in 1,2-diaminoethane with sodium methoxide in benzene-methanol using *o*-nitroaniline as indicator. Calc. for $C_{22}H_{22}N_4O_2$: C 70.6; H 5.9; N 15.0; equiv. wt. 374.4 or 187.)

4,4'-Ethylidenebis[1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one] (II h). II a (0.97 g) was dissolved in acetic acid, a few pieces of ice were added, and bromine (0.83 g) in acetic acid was poured into the solution. More ice and water precipitated the bromo compound, which was filtered, washed with water and air-dried. Yield: 1.47 g. After one crystallization from ethanol it melted at 119—120° (decomp.). The bromine was split off quantitatively at room temperature by dilute sodium hydroxide solution. (Found: C 49.4; H 3.8; N 10.6; Br 29.9; mol.wt. 520. Calc. for $C_{22}H_{20}N_4O_2Br_2$: C 49.6; H 3.8; N 10.5; Br 30.0; mol.wt. 532.)

4,4'-Propylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II b). A mixture of 1-phenyl-3-methyl-2-pyrazolin-5-one (6 g) and propionaldehyde (15 ml) was stirred until an almost clear solution was obtained. After filtration the aldehyde was evaporated under reduced pressure and the residue was recrystallized from ether. Yield of colourless crystals: 5.3 g. After recrystallization from ethanol the product melted at 152° (decomp.). (Found: C 71.1; H 6.3; N 14.4; equiv. wt. 386 on titration in ethanol — water with barium hydroxide using phenolphthalein as indicator, 197 on titration in 1,2-diaminoethane with sodium methoxide in benzene-methanol solution using *o*-nitroaniline as indicator. Calc. for $C_{23}H_{24}N_4O_2$: C 71.1; H 6.2; N 14.4; equiv. wt. 388.5 or 194.)

4,4'-Butylidenebis [1-phenyl-3-methyl-2-pyrazolin-5-one] (II c). A mixture of I (6 g) and *n*-butyraldehyde (15 ml) was shaken until an almost clear solution was obtained and was then filtered after addition of ether. In the filtrate colourless crystals separated. More ether was added and the crystals were collected by filtration and washed with ether, yield 5.5 g. After recrystallization from ethanol, the product melted at 145° (decomp.). (Found: C 71.4; H 6.5; N 13.9; equiv. wt. 398 on titration with barium hydroxide using phenolphthalein as indicator. $C_{24}H_{26}N_4O_2$ requires: C 71.6; H 6.5; N 13.9; equiv. wt. 402.5.)

*4,4'-*Iso*butylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II d)* was prepared from I (6 g) and *iso*butyraldehyde (15 ml) analogously to II c, yield 5.4 g, m.p. 210° (decomp.). (Found: C 71.4; H 6.7 ;N 14.0; equiv. wt. 398 on titration with barium hydroxide solution using phenolphthalein as indicator. $C_{24}H_{26}N_4O_2$ requires: C 71.6; H 6.5; N 13.9; equiv. wt. 402.5.)

4,4'-Heptylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II e). Heptanal (10.3 g) and I (15.1 g) were stirred overnight. The following day the excess of aldehyde and impurities were extracted with light petroleum. Colourless crystals (19 g) remained. They were recrystallized from ethanol, m.p. 134—135° (decomp.). (Found: C 72.8; H 7.2; N 12.5; equiv. wt. 439 on titration in aqueous ethanol with barium hydroxide (phenolphthalein) and 219 on titration in 1,2-diaminoethane with sodium methoxide in benzene-methanol solution (*o*-nitroaniline). Calc. for $C_{27}H_{32}N_4O_2$: C 72.9; H 7.3; N 12.6; equiv. wt. 445 or 222.)

*1-Phenyl-3-methyl-4-*iso*propylidene-2-pyrazolin-5-one (III b).* This compound has been prepared by a modification of the method of Knorr [8]. Acetone (30 ml) and I (5.0 g) were refluxed overnight. The acetone was then evaporated under reduced pressure, and the 1-phenyl-3-methyl-4-*iso*propylidene-2-pyrazolin-5-one left was recrystallized once from ethanol. Yield: 4.2 g; m.p. 116°. If the product obtained contains traces of II f, it can be purified by extraction with ether at room temperature, filtration of the extract and evaporation of the solvent at reduced pressure.

*1-Phenyl-3-methyl-4-*sec*-butylidene-2-pyrazolin-5-one (III c).* III c was prepared from methylethylketone (35 ml) and I (5.0 g) analogously to III b. Yield: 3.9 g; m.p.

88—89°. (Found: C 73.5; H 7.0; N 12.3. Calc. for $C_{14}H_{16}N_2O$: C 73.7; H 7.1; N 12.3.) The product should be stored in an ice-box.

4,4'-sec-Butylidenebis[1-phenyl-3-methyl-2-pyrazolin-5-one] (II g). I (10 g) was refluxed in methylethylketone (40 ml) for 3 h. The ketone was evaporated under reduced pressure, and the III c formed was extracted with small amounts of ether. The colourless residue (II g) was crystallized once from ethanol, m.p. 106°. Michaelis and Zilg [10] give quite a different m.p., 248°, which is, however, surprisingly high compared to the m.p. of the corresponding *iso*propylidene compound, 138° (Knorr [8]). (Found: C 71.4; H 6.5; N 13.9; O 8.0. Calc. for $C_{24}H_{26}N_4O_2$: C 71.6; H 6.5; N 13.9; O 8.0.)

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