and 15 cc. of 2-aminopropanol was refluxed for 4 hours. The alcohol which was formed was allowed to escape from the reaction mixture through an air condenser. The excess amino alcohol was removed *in vacuo*, the oily residue was dissolved in hot ethanol, the solution was treated with charcoal, filtered and the filtrate was cooled. The precipitated amide weighed 1.5 g. (88%), m.p. 220–222°.

Anal. Calcd. for $C_{17}H_{18}O_3N_2$: N, 9.46. Found: N, 9.28.

The amide, dissolved in absolute ethanol, was treated with alcoholic hydrogen chloride; when dry ether was added, the hydrochloride precipitated; m.p. 205–207° after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{17}O_3N_2Cl$: N, 8.48; Cl, 10.65. Found: N, 8.46; Cl, 10.73.

(b) The acid chloride, obtained from 24 g. of the potassium salt of the carboxylic acid, was mixed with 50 cc. of benzene and added, slowly, to 26 g. of 2-aminopropanol, dissolved in 75 cc. of benzene. The mixture was refluxed for 3 hours whereupon an oily precipitate formed. After decantation of the benzene, the oil was washed with water and then allowed to remain under 50 cc. of 10% sodium carbonate solution for several hours. The solidified material was dried and recrystallized from ethanol; m.p. 220–222°, yield 11 g. (41%).

ANN ARBOR, MICHIGAN

[COMMUNICATION NO. 1646 FROM THE KODAK RESEARCH LABORATORIES]

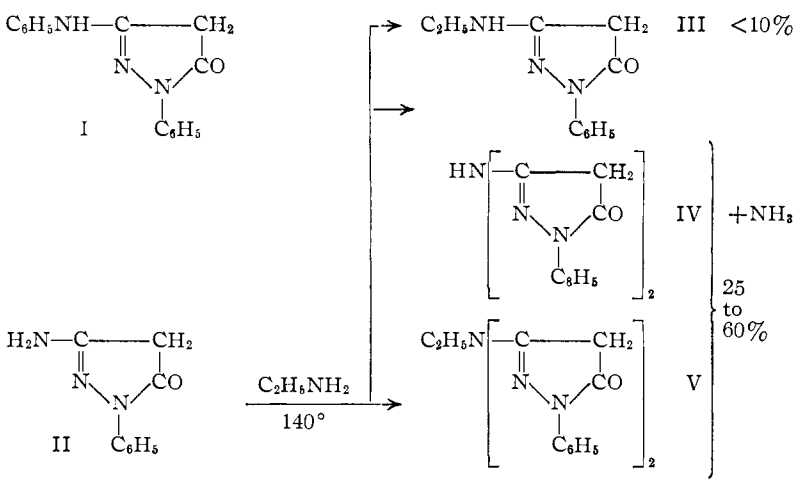
The Reaction of 1-Substituted-3-amino-5-pyrazolones with Amines

BY B. GRAHAM,[1] W. RECKHOW AND A. WEISSBERGER

RECEIVED FEBRUARY 16, 1954

The reactions are investigated which occur when 1-substituted-3-substituted-amino-5-pyrazolones are heated with primary aromatic or aliphatic amines, RNH_2. Three types of compounds are obtained, namely, 1-substituted-3-amino-5-pyrazolones, 3,3′-imino-bis-(1-substituted-5-pyrazolones) and 3,3′-R-imino-bis-(1-substituted-5-pyrazolones). The latter compounds undergo cyclization condensations with ethyl *o*-formate or formaldehyde. A yellow compound obtained in the condensation of aniline with 1-phenyl-3-amino-5-pyrazolone is probably a trimeric condensation product of the latter.

The formation of 1-phenyl-3-anilino-5-pyrazolone (I) by the action of aniline on 1-phenyl-3-amino-5-pyrazolone (II) has been described by Weissberger and Porter.[2] When an attempt was made to synthesize 1-phenyl-3-ethylamino-5-pyrazolone (III) by the reaction of II with ethylamine, III was obtained in a low yield, while the principal products were 3,3′-imino-bis-(1-phenyl-5-pyrazolone) (IV), and 3,3′-ethylimino-bis-(1-phenyl-5-pyrazolone) (V).



Similar results were obtained with *n*-butylamine, *n*-amylamine and benzylamine. When II was heated with ammonia in a sealed tube, a 70% yield of IV resulted, and 1-(4-*p*-*t*-butylphenoxy-phenyl)-3-amino-5-pyrazolone, when refluxed with *n*-butylamine, yielded 3,3′-imino-bis-[1-(4-*p*-*t*-butylphenoxy-phenyl)-5-pyrazolone] in 13% yield. The 3,3′-imino-bis-(5-pyrazolones) are high melting, rather insoluble in organic media, and react with *p*-amino-dialkylanilines in the presence of oxidizing agents to form bluish-magenta azomethine dyes.[3]

Jennen[4] prepared 3,3′-imino-bis-(1-*m*-chlorophenyl-5-pyrazolone) as a by-product in the synthesis of 1-*m*-chlorophenyl-3-amino-5-pyrazolone from *m*-chlorophenylhydrazine and ethyl β-amino-β-ethoxyacrylate.[5] A similar reaction in these Laboratories with phenylhydrazine and ethyl β-amino-β-ethoxyacrylate yielded 9% of IV and 34% of II. Ammonia was evolved during this reaction. The latter may account for the formation of IV from the principal product, II.

One might expect that cyclizations involving the reactive 4-positions of the two pyrazolone nuclei of the 3,3′-imino-bis-(5-pyrazolones) should proceed readily. Thus, 8-*n*-butyl-3,5-dioxo-2,6-diphenyl-2,3,4a,5,6,8-hexahydrodipyrazolo[3,4-b,4′,3′-e]-pyridine (VII) was obtained when *n*-butylimino-bis-(1-phenyl-5-pyrazolone) (VI) was treated with ethyl orthoformate; with formalin, 8-*n*-butyl-3,5-dioxo-2,6-diphenyl-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo-[3,4-b,4′,3′-e]pyridine (VIII) was formed.

The reaction of 1-phenyl-3-amino-5-pyrazolone (II) with aniline[2] was reinvestigated to determine whether compounds of the types IV or V were formed along with 1-phenyl-3-anilino-5-pyrazolone (I). No 3,3′-imino-bis-(1-phenyl-5-pyrazolone) (IV) was isolated when II was refluxed with aniline until no more ammonia was evolved (two hours). When the reaction was stopped after 15 minutes, a

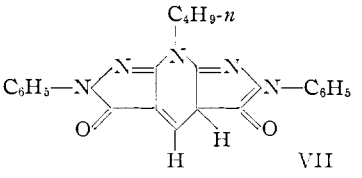
(1) Now at Stanford Research Institute, Stanford, Calif.

(2) A. Weissberger and H. D. Porter, THIS JOURNAL, **64**, 2133 (1942).

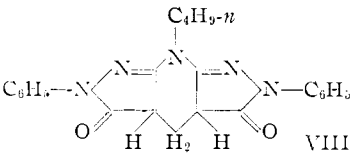
(3) A. Weissberger and H. D. Porter, *ibid.*, **65**, 52 (1943).

(4) J. J. Jennen, British Patent 636,988 (1950).

(5) B. Graham, H. D. Porter and A. Weissberger, THIS JOURNAL, **71**, 983 (1949).



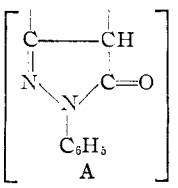
VII



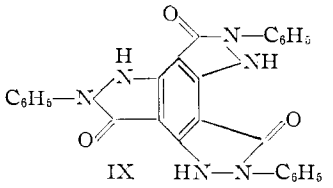
VIII

4% yield of IV was obtained while some of the starting material II was recovered. However, IV is not an intermediate in the formation of 1-phenyl-3-anilino-5-pyrazolone (I) from II, since only the starting material was recovered and no trace of I could be found when IV was refluxed with aniline for two hours. The formation of IV as a by-product is probably caused by the reaction of II with the ammonia evolved in the reaction of II with aniline.

The insoluble, yellow material mentioned by Weissberger and Porter[2] in the reaction of aniline with II was investigated further. Its analysis agrees with the empirical formula $C_9H_6N_2O$, *i.e.*, with the structural unit A. An attempted molecular weight determination failed because of the insolubility of the compound. The high melting point, > 400°, and the insolubility suggest a large symmetrical molecule, such as 3,6,9-trioxo-2,5,8-triphenyl-1,3,4,5,6,7,8,9-octahydro-2-benzo-[1.2-c,3.4-c′,5.6-c″]tripyrazole (IX).



A



IX

Experimental

3,3′-Imino-bis-(1-phenyl-5-pyrazolone) (IV).—1-Phenyl-3-amino-5-pyrazolone (II) (10 g.) and 25 g. of liquid ammonia were heated in a sealed tube at 85–90° for 20 hours. The residues from the evaporation of the ammonia were dissolved in 100 ml. of methanol and acidified with acetic acid. The fawn-colored powder was washed well with methanol, 6.6 g., 69%, m.p. 290–300°. *Anal.* Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.9; H, 4.5; N, 21.0. Found: C, 64.5, 64.5; H, 4.4, 4.5; N, 20.5, 21.1.

3,3′-Ethylimino-bis-(1-phenyl-5-pyrazolone) (V).—Fifty grams of II was heated with 140 ml. of ethylamine in sealed tubes at 130–140° for one hour. The residue from the evaporation of the amine was dissolved in 100 ml. of ethyl alcohol and the solution was acidified with acetic acid. The product, 17 g., m.p. >250°, was a mixture of IV and V. The solubilities of the two are so similar that a quantitative separation is difficult. However, analytically pure V was extracted from the mixture with boiling *n*-butyl alcohol, m.p. 265–267°. *Anal.* Calcd. for $C_{20}H_{19}N_5O_2$, V: C, 66.4; H, 5.3; N, 19.4. Found: C, 66.3, 66.4; H, 5.2, 5.3; N, 19.9, 19.4. The residue from the extraction melted at >290° and was IV.

1-Phenyl-3-ethylamino-5-pyrazolone (III).—The acetic acid–alcohol filtrates from the preparation of IV and V above were concentrated to dryness under vacuum at 100°. The residues were dissolved in 100 ml. of hot methanol. The cooled solution yielded 5 g. of mixed material, which was extracted with 20 ml. of hot methanol. About half of the material was now insoluble, so the slurry was filtered. When this filtrate was cooled, 2.5 g., 4%, of III precipitated as large rhombic crystals, m.p. *ca.* 150°. This material, III, was twice recrystallized from methanol, 1.25 g., m.p. 153–155°. *Anal.* Calcd. for $C_{11}H_{13}N_3O$: C, 65.0; H, 6.4; N, 20.7. Found: C, 64.4; H, 6.1; N, 20.7.

1-Phenyl-3-(N-ethyl)-benzamido-5-pyrazolone.—The 1-phenyl-3-ethylamino-5-pyrazolone (III), 1.25 g., was acylated with 1.82 g. of benzoyl chloride in 10 ml. of pyridine. The product was precipitated with dilute hydrochloric acid. The resulting gum was dissolved in 10 ml. of 5% alcoholic potassium hydroxide solution. This solution, after one hour at 25°, was acidified with hydrochloric acid and allowed to evaporate. The residue was triturated with benzene which caused it to crystallize. The solid was recrystallized from 50 ml. of ligroin, 1.0 g., 54%, m.p. 111–113°. *Anal.* Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.4; H, 5.5; N, 13.7. Found: C, 69.9; H, 5.4; N, 14.3.

3,3′-*n*-Butylimino-bis-(1-phenyl-5-pyrazolone) (VI).—1-Phenyl-3-amino-5-pyrazolone (175 g.) was heated at reflux for 19 hours in 500 ml. of *n*-butylamine. The amine was removed under vacuum at 100°, and the residual oil was taken up in 500 ml. of hot methanol and acidified with acetic acid. A precipitate collected from the hot solution was analytically pure IV, 61.5 g., 37%. The cooled solution yielded 30 g. of VI. This was recrystallized from 800 ml. of 3-A alcohol to give 17.5 g., 9.0%, m.p. 233–237°. *Anal.* Calcd. for $C_{22}H_{23}N_5O_2$: C, 67.9; H, 5.9; N, 18.0. Found: C, 68.1; H, 5.9; N, 18.3.

3,3′-*n*-Amylimino-bis-(1-phenyl-5-pyrazolone).—A reaction similar to the preceding one was carried out using *n*-amylamine. IV was produced in 26% yield, while 3-*n*-amylimino-bis-(1-phenyl-5-pyrazolone), after recrystallization from *n*-butyl alcohol, was formed in 15% yield, m.p. 227–230°. *Anal.* Calcd. for $C_{23}H_{25}N_5O_2$: C, 68.4; H, 6.2; N, 17.4. Found: C, 68.1; H, 6.2; N, 17.3.

3,3′-Benzylimino-bis-(1-phenyl-5-pyrazolone).—1-Phenyl-3-amino-5-pyrazolone (20 g.) in 25 ml. of benzylamine was heated at 100° for three days. The benzylamine was removed under vacuum. The residue was dissolved in 50 ml. of methanol and acidified. The product, 4.0 g., 8%, was recrystallized from *n*-butyl alcohol, m.p. 245–247°. *Anal.* Calcd. for $C_{25}H_{21}N_5O_2$: C, 70.9; H, 5.0; N, 16.5. Found: C, 70.2; H, 5.2; N, 16.3.

3,3′-Imino-bis-(1-*p*-*t*-butylphenoxyphenyl-5-pyrazolone).—1-*p*-*t*-Butylphenoxyphenyl-3-amino-5-pyrazolone[6] (32 g.) was heated at reflux in 100 ml. of *n*-butylamine for 18 hours. The amine was removed under vacuum and the residue was dissolved in 100 ml. of methanol. The acidified solution yielded 8 g., 13%, of the bis-pyrazolone, which was recrystallized from *n*-butyl alcohol, m.p. 260–265°. *Anal.* Calcd. for $C_{38}H_{39}N_5O_4$: C, 72.6; H, 6.2; N, 11.1. Found: C, 72.1; H, 6.0; N, 11.1.

8-*n*-Butyl-3,5-dioxo-2,6-diphenyl-2,3,4a,5,6,8-hexahydrodipyrazolo[3,4-b,4′-3′-e]pyridine (VII).—A solution of 2 g. of VI in 100 ml. of ethyl orthoformate was refluxed for 30 minutes. The cooled solution yielded 1.1 g. of VII, m.p. > 300°. This was recrystallized from 100 ml. of acetic acid as 1.0 g. of yellow dye. *Anal.* Calcd. for $C_{21}H_{21}N_5O_2$: C, 69.3; H, 5.3; N, 17.6. Found: C, 69.2; H, 5.3; N, 17.9.

8-*n*-Butyl-3,5-dioxo-2,6-diphenyl-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b,4′,3′-e]pyridine (VIII).—One gram of VI was dissolved in a solution of 3 ml. of 30% formalin and 100 ml. of acetic acid. The mixture was refluxed for one hour. Since no precipitate formed upon cooling, the product was diluted with water. The resulting yellow solid was washed with hot alcohol which removed the yellow color. The white material was recrystallized from *n*-butyl alcohol, 0.5 g., white granules, m.p. 267–269°. *Anal.* Calcd. for $C_{23}H_{23}N_5O_2$: C, 69.0; H, 5.7; N, 17.4. Found: C, 69.6; H, 5.7; N, 17.6.

The Reaction of 1-Phenyl-3-amino-5-pyrazolone (II) with Aniline.[2]—A solution of 20 g. of II in 50 ml. of aniline was refluxed over a flame. After 15 minutes, one-half (A) of the solution was withdrawn for examination. The remainder (B) was refluxed for a total of 1.75 hours. A, when cooled, yielded 6.1 g. of crude, solid material, which was treated with 200 ml. of boiling absolute alcohol and filtered. The residue, 0.35 g. of gray material, m.p. >250°, was dissolved in 25 ml. of 3% sodium carbonate solution. The filtered

(6) H. D. Porter and A. Weissberger, U. S. Patent 2,369,489 (Feb. 13, 1945).

solution, when acidified, yielded 0.25 g. of IV. *Anal.* Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.9; H, 4.5; N, 21.0. Found: C, 64.5; H, 4.4; N, 21.1. The cooled alcoholic liquor from A yielded 4.1 g. of starting material II, m.p. 215–220°.

The half of the material, B, which was refluxed longer, yielded the same products as described in the literature,[2] *i.e.*, I and some alcohol-insoluble yellow material. The insoluble yellow product IX (needles), 0.26 g., m.p. >400° (darkens > 360°), was washed with hot alcohol and submitted for analysis without being recrystallized, since no solvent could be found for the material. *Anal.* Calcd. for $C_{27}H_{18}N_6O_3$, IX: C, 68.4; H, 3.8; N, 17.7. Found: C, 68.5; H, 4.0; N, 17.7. No IV was isolated. An attempt was made to acylate the insoluble yellow material IX. It failed to dissolve in boiling 50% acetic anhydride–pyridine solution.

1-Phenyl-3-*p*-toluidino-5-pyrazolone (X).—A solution of 20 g. of II in 50 g. of *p*-toluidine, after being refluxed two hours, was diluted with 100 ml. of chloroform and cooled. The product was collected, washed well with chloroform, and recrystallized twice from 300-ml. portions of ethanol. Again a small yield (1.0 g.) of insoluble yellow needles (IX) was obtained, m.p >400°. *Anal.* Found: C, 68.0; H, 3.9; N, 17.0. The yield of X was 7.0 g., 23%, m.p. 220–223°. *Anal.* Calcd. for $C_{16}H_{15}N_3O$: N, 15.9. Found: N, 15.8.

1-Methyl-3-anilino-5-pyrazolone[7] (XI).—A solution of 1.0 g. of 1-methyl-3-amino-5-pyrazolone[5] in 3.0 ml. of aniline was refluxed 1.5 hours. The cooled solution yielded 0.4 g. of crude material, which was washed well with methanol. When this was treated with 20 ml. of boiling acetonitrile, 0.1 g. failed to dissolve. This material turns blue in the coupling test and is probably a mixture of compounds of types IV and IX. The cooled acetonitrile yielded 0.2 g., 14%, of XI, m.p. 220–222°. *Anal.* Calcd. for $C_{10}H_{11}N_3O$: C, 63.5; H, 5.8; N, 22.2. Found: C, 63.9; H, 5.5; N, 22.1.

The Reaction of 3,3'-Imino-bis-(1-phenyl-5-pyrazolone) (IV) with Aniline.—One gram of IV was suspended in 5 ml. of refluxing aniline for two hours. The material failed to dissolve and 0.7 g. was recovered from the cooled mixture. No other workable product was found.

(7) A. Weissberger and H. D. Porter, THIS JOURNAL, **65**, 732 (1943).

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

Vitamin B_{12}. XXIII. Resolution of DL-1-Amino-2-propanol

BY ROBERT L. CLARK, WILLIAM H. JONES, WILLIAM J. RAICH AND KARL FOLKERS

RECEIVED FEBRUARY 10, 1954

DL-1-Amino-2-propanol was resolved into $D_g(-)$-1-amino-2-propanol and $L_g(+)$-1-amino-2-propanol by the following sequence of compounds and steps: DL-1-benzylamino-2-propanol, DL-2-(1-benzylaminopropyl)-*p*-nitrobenzoate and resolution of L(+)-tartrates, saponification to D(−)- and L(+)-1-benzylamino-2-propanol, hydrogenation to the D- and L-1-amino-2-propanols.

The "ninhydrin-reacting" substance was first recognized[1] in an acid hydrolysate of vitamin B_{12}. This substance was detected and studied by paper strip techniques, and it was indistinguishable from 2-amino-1-propanol.[2] The identification of the substance with 2-amino-1-propanol was invalidated when it was oxidized with permanganate and did not give alanine.[3]

The structure of this substance reacting with ninhydrin was established[4] as 1-amino-2-propanol (I) by isolation of a dibenzoate of the amino alcohol and its characterization and degradation. Structure I was confirmed by synthesis.[4] This synthetic route was chosen because it would establish configuration; it showed that the substance is D_g-1-amino-2-propanol. D_g-Lactic acid was converted to D_g-1-amino-2-propanol by esterification, conversion to the amide and reduction with lithium aluminum hydride.

The first determinations[5] of the amount of the aminopropanol liberated in the hydrolysis of vitamin B_{12} indicated two moles per molecule of vitamin B_{12}. The analytical method was based upon a quantitative determination of ethanolamine. Later determinations[6] of the liberated D_g-1-amino-2-propanol have led to the statement that there is only one molecule of the substance per molecule of vitamin B_{12}. This conclusion is based upon the results of two methods: (a) quantitative measurement of the ninhydrin reaction product by comparison of absorption with controls; (b) differential determination of ammonia and "total ammonia" after formation of ammonia from 1-amino-2-propanol by periodate oxidation.

The most recent report[7] on the amount of liberated 1-amino-2-propanol confirmed the data of Cooley, *et al.*,[6] for the same hydrolytic conditions, but stronger acid hydrolysis in some experiments gave results approximating two moles of 1-amino-2-propanol. Nevertheless, these investigators[7] favored the conclusion[6] on one mole and gave no explanation of the high "anomalous" results.

The value of the synthesis[4] of D_g-1-amino-2-propanol was confirmation of structure and configuration, but not for convenient preparation. DL-1-Amino-2-propanol is available commercially; therefore, it was desirable to study methods for its resolution. No procedures for the resolution of DL-1-amino-2-propanol could be found in the literature.

Although several salts of the aminopropanol were examined for possible direct resolution, none of them crystallized. A derivative was prepared by which resolution was accomplished with salts of $L(^+)$-tartaric acid.

DL-1-Amino-2-propanol reacted with benzaldehyde and the Schiff base was hydrogenated with

(1) B. Ellis, V. Petrow and G. F. Snook, *J. Pharm. Pharmacol.*, **1**, 60 (1949).

(2) B. Ellis, V. Petrow and G. F. Snook, *ibid.*, **1**, 735 (1949); **1**, 950 (1949).

(3) G. Cooley, B. Ellis and V. Petrow, *ibid.*, **2**, 128 (1950).

(4) D. E. Wolf, W. H. Jones, J. Valiant and K. Folkers, THIS JOURNAL, **72**, 2820 (1950).

(5) E. Chargaff, C. Levine, C. Green and J. Kream, *Experientia*, **6**, 229 (1950).

(6) G. Cooley, M. T. Davies, B. Ellis, V. Petrow and B. Sturgeon *J. Pharm. Pharmacol.*, **4**, 257 (1953).

(7) J. B. Armitage, J. R. Cannon, A. W. Johnson, L. F. J. Parker, E. L. Smith, W. H. Stafford and A. R. Todd, *J. Chem. Soc.*, 3849 (1953).