235–236°, identical in infrared spectrum (KBr) with starting material. Finally, 10–100% methanol in chloroform eluted 34 mg. of an oil which on examination by paper chromatography appeared to consist of both crinamidine and epicrinamidine. Accordingly, it was carefully rechromatographed over Florisil with methanol–chloroform, and the two components were separated, One product was identified as crinamidine. With this crinamidine removed, the second component was found by infrared examination most nearly to resemble powelline, and the absence of epicrinamidine was established.

Conversion of Dihydrohaemanthamine to (+)-Dihydrobuphanisine.—A solution of 521 mg. of dihydrohaemanthamine in 5 ml. of thionyl chloride was refluxed for 1.5 hours. The solvent was removed under reduced pressure, and the resulting gum was taken up in 20 ml. of tetrahydrofuran. Lithium aluminum hydride (1.0 g.) was added, and the mixture was refluxed for 5 hours. The excess hydride was decomposed by the addition of ethanol, and 50% sodium hydroxide was added to destroy the complex. The tetrahydrofuran was decanted. The precipitate was washed with chloroform, and the washings were combined with the tetrahydrofuran. Evaporation of the dried solvents left 434 mg. of crude product which was chromatographed over alumina that had been deactivated with ethyl acetate. Pure benzene eluted a few milligrams of an odoriferous thio compound. Ethyl acetate in benzene (3–100%) afforded 344 mg. of crystalline (+)-dihydrobuphanisine. Further elution with 5% ethanol in ethyl acetate produced 46 mg. (9%) of dihydrohaemanthamine.

The (+)-dihydrobuphanisine was recrystallized from ether, m.p. 95–97°. On admixture with authentic (−)-dihydrobuphanisine, the melting point was depressed below 70° while the infrared spectrum (KBr) was identical with that of authentic (−)-dihydrobuphanisine. (+)-Dihydrobuphanisine showed $[\alpha]^{25}_{589}$ +27.9°, $[\alpha]^{25}_{436}$ +61.4°, $[\alpha]^{25}_{400}$ +83°, $[\alpha]^{25}_{350}$ +162° (*c* 0.59, chloroform). Authentic (−)-dihydrobuphanisine showed $[\alpha]^{25}_{589}$ −27.9°, $[\alpha]^{25}_{436}$ −61.7°, $[\alpha]^{25}_{400}$ −83.3°, $[\alpha]^{25}_{350}$ −164° (*c* 0.66, chloroform).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37. Found: C, 71.19; H, 7.38.

Crinine (II), R.D.: $[\alpha]^{25}_{650}$ −17°, $[\alpha]^{25}_{589}$ −23.5°, $[\alpha]^{25}_{436}$ −91.7°, $[\alpha]^{25}_{360}$ −302°, $[\alpha]^{25}_{330}$ −694° (*c* 0.64, chloroform).

Buphanisine (III), R.D.: $[\alpha]^{25}_{650}$ −24.7°, $[\alpha]^{25}_{589}$ −32.4°, $[\alpha]^{25}_{436}$ −102°, $[\alpha]^{25}_{360}$ −308°, $[\alpha]^{25}_{330}$ −639° (*c* 0.85, chloroform).

(−)-Crinane (I), R.D.: $[\alpha]^{25}_{589}$ −14°, $[\alpha]^{25}_{436}$ −32°, $[\alpha]^{25}_{370}$ −70°, $[\alpha]^{25}_{330}$ −221° (*c* 0.20, chloroform).

(+)-Powellane (V), R.D.: $[\alpha]^{25}_{589}$ 0°, $[\alpha]^{25}_{436}$ +10°, $[\alpha]^{25}_{360}$ +44°, $[\alpha]^{25}_{320}$ +117° (*c* 0.25, chloroform).

Conversion of Dihydrobuphanidrine to Dihydrobuphanisine.—An ethanolic solution of 1.92 g. of buphanidrine, m.p. 90–91°, $[\alpha]^{26}_{589}$ −4.7° (*c* 1.1, chloroform), was hydrogenated in the presence of 330 mg. of 5% palladium-on-charcoal. After absorption ceased, the catalyst was removed by filtration. Concentration of the filtrate gave 2.0 g. of oil which was purified *via* the picrate, m.p. 284–285° dec. (reported[5] for dihydrobuphanidrine picrate, m.p. 281–283° dec.). The free base, 1.9 g., was regenerated from the picrate by passing a chloroform solution of the picrate through a column of alumina. The chloroform eluates were concentrated and a portion was purified by evaporative distillation at 130° (10 μ), $[\alpha]^{26}_{589}$ −10.6°, $[\alpha]^{26}_{436}$ −14.2° (*c* 0.85, chloroform). The remaining 1.7 g. of dihydrobuphanidrine was dissolved in 100 ml. of xylene and treated with 2.0 g. of sodium and 17 ml. of isoamyl alcohol by the procedure reported earlier.[12] From the alkaloids forming chloroform-insoluble hydrochlorides there was obtained a mixture of dihydrobuphanidrine and dihydrobuphanisine. The alkaloid fraction forming chloroform-soluble hydrochlorides (1.3 g.) appeared to consist entirely of dihydrobuphanidrine and this was retreated with 2.0 g. of sodium and 20 ml. of isoamyl alcohol.[32] The product appeared to be a mixture of dihydrobuphanidrine and dihydrobuphanisine. The combined products were partially separated by chromatography on alumina. Elution with benzene–ethyl acetate (1:1) and ethyl acetate gave first 188 mg. of dihydrobuphanidrine followed by 560 mg. of a mixture of dihydrobuphanidrine and dihydrobuphanisine. Elution with 20% ethanol in ethyl acetate gave 300 mg. of material with an infrared spectrum identical with that of dihydrobuphanisine. Crystallization from ether gave 180 mg. of IV, m.p. 94–95°, $[\alpha]^{24}_{589}$ −26°, $[\alpha]^{25}_{436}$ −61° (*c* 0.71, chloroform). A mixture melting point determination with authentic (−)-dihydrobuphanisine,[12] m.p. 95–96°, was not depressed.

(32) Quantitative estimates of the ratio of dihydrobuphanidrine and dihydrobuphanisine can be made from the intensity of the infrared absorption at 6.18 μ shown only by the former compound: *cf.* W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 4807 (1955).

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE UNIVERSITY]

The Formation of 1-(2,4-Dinitrophenyl)-substituted Pyrazolines from α,β-Unsaturated 2,4-Dinitrophenylhydrazones

BY WILLIAM L. CHAMBERS AND M. L. WILLARD

RECEIVED SEPTEMBER 25, 1959

The formation of 1-(2,4-dinitrophenyl)-substituted pyrazolines from α,β-unsaturated 2,4-dinitrophenylhydrazones has been demonstrated. An alternate synthesis of 1-(2,4-dinitrophenyl)-substituted pyrazolines is presented.

The formation of 1-(2,4-dinitrophenyl)-substituted pyrazolines from α,β-unsaturated 2,4-dinitrophenylhydrazones has been proposed by several workers,[1] but experimental proof of this formation has not been presented.

When α-bromopropiophenone 2,4-dinitrophenylhydrazone is refluxed in glacial acetic acid, dehydrohalogenation takes place, and an orange product (I), m.p. 214–216°, is produced. Ramirez and Kirby[2] eliminated a pyrazoline structure for this compound on the basis that phenyl vinyl ketone DNPH was stable under ring closing conditions. These workers noted also that the ultraviolet absorption spectrum of compound (I) compared favorably with that of an azo structure.

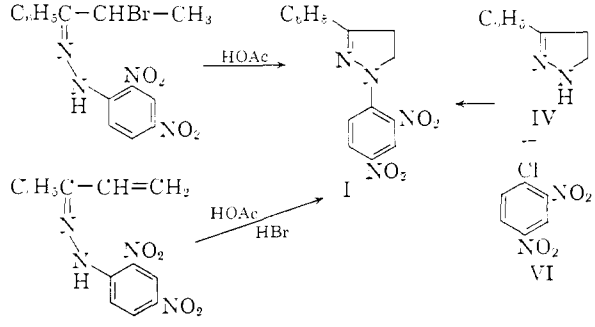
We find, however, that when phenyl vinyl ketone DNPH is treated with boiling glacial acetic acid containing hydrobromic acid, the same orange product (I) was obtained.

To establish the presence of a pyrazoline structure, the heterocyclic was synthesized by an alternate route from 2,4-dinitrochlorobenzene (VI) and 3-phenyl-2-pyrazoline (IV). This reaction yielded

(1) (a) G. Morgan and C. F. Griffith, *J. Chem. Soc.*, 841 (1937); (b) C. F. H. Allen and J. H. Richmond, *J. Org. Chem.*, **2**, 222 (1937); (c) T. L. Jacobs in R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. 5, p. 64; (d) L. I. Braddock, K. Y. Garlow, L. I. Grim, A. F. Kirkpatrick, S. W. Pease, A. J. Pollard, E. F. Price, T. L. Reissman, N. A. Rose and M. L. Willard, *Anal. Chem.*, **25**, 301 (1953); (e) D. S. Tarbell and W. E. Lovett, THIS JOURNAL, **78**, 2259 (1956).

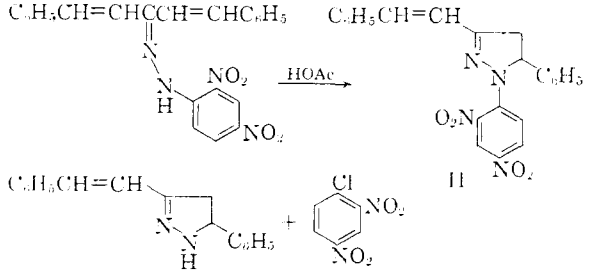
(2) Fausto Ramirez and Arthur F. Kirby, *ibid.*, **75**, 6026 (1953).

an orange product identical with those of the first two reactions in all respects. After this phase of the investigation had begun, this type of pyrazoline synthesis was reported by Mousseron and co-workers,[3] although no experimental details were published.

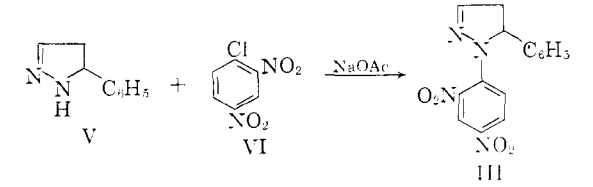


It was also observed that cinnamaldehyde DNPH was unaltered by treatment with acetic acid which contained hydrobromic acid. To demonstrate the possibility that ring closure fails in this case because the *anti* isomer required by steric considerations was not at hand, it was decided to investigate the behavior of dibenzalacetone DNPH under ring closing conditions. Should dibenzalacetone DNPH undergo ring closure, it would seem likely that cinnamaldehyde DNPH ought to form a pyrazoline, providing the *anti* isomer were present.

Treatment of dibenzalacetone DNPH with boiling acetic acid was found to yield an isomeric compound (II). This isomer was identical with the product of the reaction between 2,4-dinitrochlorobenzene and 3-styryl-5-phenyl-2-pyrazoline. When hydrobromic acid was present in the acetic acid, the formation of the pyrazoline (II) from dibenzalacetone DNPH was accelerated.



The product which would be formed on ring closure of cinnamaldehyde DNPH is 1-(2,4-dinitrophenyl)-5-phenyl-2-pyrazoline (III). This compound was obtained when 5-phenyl-2-pyrazoline (V) and 2,4-dinitrochlorobenzene (VI) were refluxed in absolute ethanol in the presence of fused sodium acetate. The yellow product melted at 157–158°.



When 5-phenyl-2-pyrazoline (V) and 2,4-dinitrochlorobenzene (VI) are refluxed in ethanol or allowed to react in ethereal solution in the absence of sodium acetate, the product is 1-(2,4-dinitrophenyl)-3-phenyl-2-pyrazoline (I). Evidently the hydrogen chloride evolved rapidly isomerized the unreacted 5-phenyl-2-pyrazoline (V) to 3-phenyl-2-pyrazoline (IV).

This product (I) was apparently obtained by Mousseron and co-workers[3] when they treated 5-phenyl-2-pyrazoline with 2,4-dinitrochlorobenzene in ethanol. The physical properties which they reported for 1-(2,4-dinitrophenyl)-5-phenyl-2-pyrazoline (m.p. 207–208°, $\lambda_{max}^{CHCl_3}$ 412 mμ and log ε 4.34) are actually those of 1-(2,4-dinitrophenyl)-3-phenyl-2-pyrazoline, which are m.p. 213–215°, $\lambda_{max}^{CHCl_3}$ 412 mμ and log ε 4.52.

Experimental[4]

Treatment of α-Bromopropiophenone DNPH with Glacial Acetic Acid.—A solution of 2.7 g. (0.007 mole) of α-bromopropiophenone DNPH in 8 ml. of glacial acetic acid was refluxed 5 minutes, repeating the work of Ramirez and Kirby.[2] The crude product was recrystallized 3 times from ethyl acetate to give 0.5 g. (24%) of orange plates, m.p. 214–216°. The infrared spectrum showed no NH peak at 3.07 μ (3257 cm.$^{-1}$).

Treatment of Phenyl Vinyl Ketone DNPH with Glacial Acetic Acid and Hydrobromic Acid.—A solution of 0.5 g. (0.002 mole) of phenyl vinyl ketone DNPH in 100 ml. of glacial acetic acid containing 0.7 ml. of 34% hydrobromic acid was refluxed 2 hours. The solution was concentrated to 30 ml. and cooled. The crude material which was recovered, m.p. 212–214°, was recrystallized from ethyl acetate to give 0.2 g. (40%), orange plates, m.p. 213–215°. This product did not depress the melting point of the product obtained by the treatment of α-bromopropiophenone DNPH with glacial acetic acid. The infrared spectrum showed no NH peak at 3.07μ (3257 cm.$^{-1}$).

Reaction of 2,4-Dinitrochlorobenzene with 3-Phenyl-2-pyrazoline.—The 3-phenyl-2-pyrazoline which was used distilled at 145–155° (10 mm.); the nitroso derivative, m.p. 149–151°, and the picrate, m.p. 151–153°, were prepared to identify the pyrazoline.[5] A solution of 15 g. (0.1 mole) of 3-phenyl-2-pyrazoline in 100 ml. of ether was mixed with 21 g. (0.1 mole) of 2,4-dinitrochlorobenzene dissolved in 100 ml. of ether. After 2 days the product was filtered and dried. The crude material, which melted from 159–185°, was recrystallized from acetic acid to give 12.5 g. (40%) of orange plates, m.p. 213–215°. The infrared spectrum (2–15 mμ) was identical with that of the product which was obtained by the treatment of phenyl vinyl ketone DNPH with acetic acid containing hydrobromic acid.

Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.81, 57.11; H, 3.87, 3.51; N, 17.63.

Treatment of Cinnamaldehyde DNPH with Acetic Acid and Hydrobromic Acid.—A solution of 1.1 g. (0.003 mole) of cinnamaldehyde DNPH, m.p. 249–251°, in 200 ml. of acetic acid containing 0.25 ml. of 48% hydrobromic acid was refluxed 6 hours and then cooled. The material which separated was collected and dried to give 1.0 g. (91%), m.p. 250–251°. This material did not depress the melting point of a sample of the starting material.

Treatment of Dibenzalacetone DNPH with 90% Acetic Acid.—A solution of 1.2 g. (0.003 mole) of dibenzalacetone DNPH in 150 ml. of 90% acetic acid was refluxed for 52 hours. The solution was concentrated to 50 ml. and water

(3) M. Mousseron, R. Jacquier and J. Brun, *Compt. rend.*, **247**, 617 (1958).

(4) Melting points are uncorrected. The analyses were done by Galbraith Laboratories, Knoxville, Tenn. All infrared spectra were obtained with a Perkin-Elmer, model 21, automatic-recording spectrophotometer. The materials were incorporated in potassium bromide pellets. The extinction coefficient of 1-(2,4-dinitrophenyl)-3-phenyl-2-pyrazoline was calculated from measurements obtained by means of a Beckman, model DU, spectrophotometer. The ultraviolet spectra of the stereoisomeric cinnamaldehyde 2,4-dinitrophenylhydrazones were obtained by means of a Warren Spectrocord.

(5) K. V. Auwers and P. Heimke, *Ann.*, **458**, 186 (1927).

was added to incipient crystallization. The crude product, m.p. 175–205°, was recrystallized once from acetic acid to give 0.3 g. (25%), orange needles, m.p. 210–212°.

Treatment of Dibenzalacetone DNPH with 90% Acetic Acid and Hydrobromic Acid.—A solution of 1.2 g. (0.003 mole) of dibenzalacetone DNPH in 150 ml. of 90% acetic acid containing 0.25 ml. of 48% hydrobromic was refluxed 6.5 hours. The solution was concentrated to 50 ml. and water was added to incipient crystallization. The crude product, m.p. 207–210°, was recrystallized from acetic acid to give 0.7 g. (58%), orange needles, m.p. 212–214°. The infrared spectrum showed no NH peak at 3.07 μ (3257 cm.$^{-1}$).

Reaction of 2,4-Dinitrochlorobenzene with 3-Styryl-5-phenyl-2-pyrazoline.—The 3-styryl-5-phenyl-2-pyrazoline which was used was a crude pale-yellow viscous oil; the N-nitroso derivative, m.p. 149–150°, was prepared to identify the pyrazoline.[6] A solution of 7.5 g. (0.030 mole) of 3-styryl-5-phenyl-2-pyrazoline in 100 ml. of ethanol was added to a solution of 6.8 g. (0.034 mole) of 2,4-dinitrochlorobenzene in 100 ml. of ethanol. The mixture was refluxed 2 hours during which time it turned deep red. After much of the solvent was removed, the material was refrigerated. The deep-red crude product which was recovered was taken up in hot ethanol, from which an orange product, m.p. 207–209°, was recovered. The crude product was recrystallized from ethyl acetate to give 6.1 g. (59%), orange crystals, m.p. 212–213°. This product did not depress the melting point of the product obtained by the treatment of dibenzalacetone DNPH with acetic acid. The infrared spectra (2–15 μ) of these products were identical.

Anal. Calcd. for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 67.73, 67.32; H, 4.36, 3.34; N, 12.85.

Reaction of 2,4-Dinitrochlorobenzene with 5-Phenyl-2-pyrazoline in Absolute Ethanol in the Presence of Fused Sodium Acetate.—The 5-phenyl-2-pyrazoline which was used was a colorless oil and distilled at 120–124° (1 mm.); the picrate derivative, m.p. 115–116°, was prepared to identify the pyrazoline.[5] A solution of 6.0 g. (0.041 mole) of 5-phenyl-2-pyrazoline in 25 ml. of absolute ethanol was added to a solution of 8.5 g. (0.042 mole) of 2,4-dinitrochlorobenzene in 350 ml. of absolute ethanol containing 4 g. of fused sodium acetate. The solution was refluxed for a period of 3.5 hours and then cooled. The sodium chloride which came down was filtered off and the solution was concentrated to about 50 ml. A red oil came down which after 24 hours crystallized. The crude product was recrystallized first from methanol and then from acetic acid to give 6.3 g. (49%), yellow crystals, m.p. 157–158°. The infrared spectrum showed no NH peak at 3.07 μ (3257 cm.$^{-1}$).

Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.33, 57.34; H, 3.79, 3.79; N, 17.89.

When, on the other hand, 2,4-dinitrochlorobenzene and 5-phenyl-2-pyrazoline were treated in 95% ethanol in the absence of sodium acetate, an orange product, m.p. 214–217°, was obtained. This material did not depress the melting point of 1-(2,4-dinitrophenyl)-3-phenyl-2-pyrazoline.

Preparation of the Low-melting Isomer of Cinnamaldehyde DNPH.—A mixture of 10 g. (0.05 mole) of 2,4-dinitrophenylhydrazine in a sixfold excess of cinnamaldehyde was allowed to react at room temperature. After an hour the excess cinnamaldehyde with the dissolved derivative was separated by suction filtration. To the filtrate was added 200 ml. of ethanol, followed by 200 ml. of a 1:1 mixture of water–ethanol. The voluminous orange precipitate was collected and dried. The crude product was recrystallized from benzene to give a low yield of orange needles, m.p. 196–197°. The melted material solidified and re-melted at 248–250°. The low-melting derivative was quantitatively converted to the high-melting derivative when treated with hot acetic acid. The ultraviolet spectra in chloroform of the materials were different. The infrared spectra of these isomeric cinnamaldehyde derivatives were almost identical from 3 to 8 μ. The region from 8 to 15 μ showed variations in the positions and in the intensities of the corresponding absorption peaks.

(6) N. Kishner, *Chem. Zentr.*, **88, II,** 318 (1916).

UNIVERSITY PARK, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN SCHOOL OF PHARMACY]

The Quasi-Favorskii Rearrangement. II.[1] Stereochemistry and Mechanism

BY EDWARD E. SMISSMAN AND GILBERT HITE[2,3]

RECEIVED MAY 4, 1959

The skeletal rearrangement of (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV) provides a means by which the mechanism and the stereochemistry of the quasi-Favorskii rearrangement may be studied. The (−)-α-halogenated ketone IV afforded racemic rearrangement acid X and residually dextrorotatory α-hydroxy ketone VI. Both chemical evidence and optical rotatory dispersion (o.r.d.) studies indicate that the rearrangement is intermediated by ion pairs. A unified mechanism has been presented for the skeletal rearrangement of α-halogenated ketones possessing no α-hydrogen (the quasi-Favorskii rearrangement).

Stevens and Farkas[4] have obtained 1-phenylcyclohexanecarboxylic acid (III) from the rearrangement of α-chlorocyclohexyl phenyl ketone (I) with powdered sodium hydroxide in refluxing xylene. To explain the high yield (53%) of rearrangement acid III, they have suggested a surface-catalyzed reaction in which the anionoid transition state is formed by initial nucleophilic attack of a hydroxide ion at the carbonyl carbon of the α-halogenated ketone I. Tchoubar and Sackur[5] were the first to observe this reaction. They favored a similar semi-benzilic rearrangement in which the migrating and the departing groups and the two continguous carbon atoms might be expected to be planar with the groups *trans*.[6] Equally as important as the mechanistic sequence is the tangible but unobservable (in this case) stereochemical result predicted by these[4,5] rationalizations: that is, inversion at the reaction terminus.

With the realization of the rearrangement of (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV), it became possible, for the first time, to observe the

(1) For the first paper in this series, see: E. E. Smissman and G. Hite, THIS JOURNAL, **81**, 1201 (1959).

(2) This and the previous publication comprise a portion of the thesis presented by G. H. in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Chemistry at the University of Wisconsin. Recipient of the Lunsford Richardson Pharmacy Award, First Prize, Central Section, 1959.

(3) This work was presented, in part, at the 135th Meeting of the American Chemical Society in Boston, Mass., April, 1959.

(4) C. L. Stevens and E. Farkas, THIS JOURNAL, **74**, 5352 (1952).

(5) B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

(6) D. Y. Curtin and P. I. Pollak, THIS JOURNAL, **73**, 992 (1951).