[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

The Reaction of α-Acylsuccinic Esters With Hydrazine

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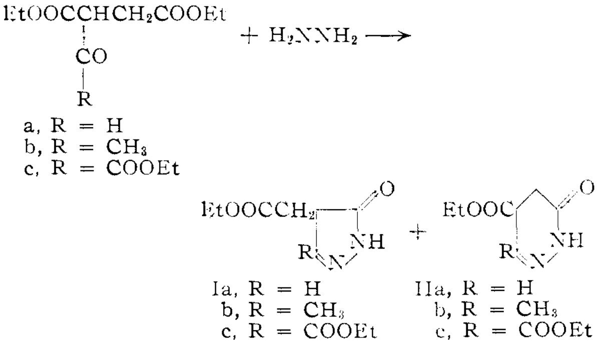
It has been shown that α-acylsuccinic esters react with hydrazine to form both pyrazolones and the isomeric dihydropyridazones; several of these isomeric pairs have been prepared, separated and their structures ascertained.

As early as 1893, von Rothenberg[1,2] reported that diethyl formylsuccinate reacted with hydrazine hydrate to yield a compound, melting at 171.5–172°, that he formulated[2] as 4-carbethoxy-4,5-dihydro-6-pyridazone. At about the same time, Curtius[3] observed that the reaction of diethyl acetylsuccinate with hydrazine gave a compound, melting at 166°, that he formulated as 3-methyl-4-carbethoxymethyl-5-pyrazolone. More recently De and Dutt[4] obtained, from the reaction of diethyl acetylsuccinate and semicarbazide, a compound containing 15.00% nitrogen and melting at 220°, that they said, without further evidence, was 3-methyl-4-carbethoxy-4,5-dihydro-6-pyridazone. Sonn[5] commented in 1935 that the compound reported by von Rothenberg[2] to be a dihydropyridazone was undoubtedly the isomeric pyrazolone. And very recently, Gault[6] has reported the reaction of triethyl oxalylsuccinate with hydrazine hydrate to give a product, melting at 155–156°, that was formulated as 3,4-dicarbethoxy-4,5-dihydro-6-pyridazone. In none of the above-mentioned papers was the structure of the products unequivocally established and in each case the choice of structure (pyrazolone or dihydropyridazone) was rather arbitrarily made. Because there was obviously considerable confusion over what is actually formed when an α-acylsuccinic ester is allowed to react with hydrazine, our purpose in this research was to repeat each of the above-mentioned reactions and investigate the nature of the products formed.

We have allowed hydrazine hydrate to react with each of the three α-acylsuccinic esters: (1) diethyl formylsuccinate, (2) diethyl acetylsuccinate and (3) triethyl oxalylsuccinate. From each of these reactions we have isolated two isomeric compounds: one a moderately high melting, less soluble, easily purified material that is a pyrazolone (I); the other a lower melting, more soluble, more difficultly purified material that has been proved to be a dihydropyridazone (II). Compound IIb was separated by fractional crystallization, whereas compounds IIa and IIc were distilled, after which compound IIc then was crystallized easily; compound IIa was an oil that was not obtained completely pure and in one instance the distilled material was found to contain about 20% of the dehydrogenated material IIIa. This is the first recorded instance of a spontaneous thermal dehydrogenation of a dihydropyridazone.

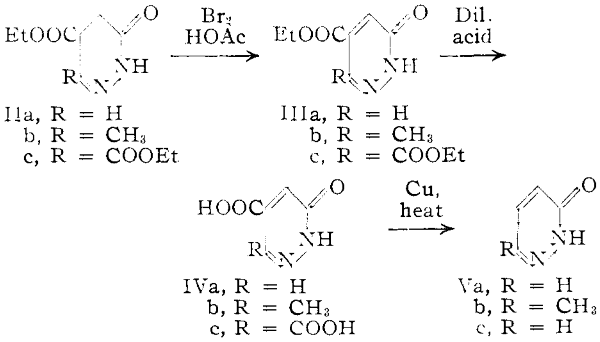


a, R = H
b, R = CH_3
c, R = COOEt

Ia, R = H
b, R = CH_3
c, R = COOEt

IIa, R = H
b, R = CH_3
c, R = COOEt

Each of the compounds IIa, IIb and IIc, when treated with bromine in glacial acetic acid, underwent dehydrogenation, a well-known reaction of dihydropyridazones,[7] to yield IIIa, IIIb and IIIc. These pyridazone esters were hydrolyzed with dilute acid, giving the corresponding pyridazone carboxylic acids, IVa, IVb and IVc. The diacid IVc underwent partial decarboxylation during the hydrolysis, as indicated by its carbon and hydrogen analysis and its neutralization equivalent. Thermal decarboxylation of these acids in the presence of a little copper powder gave 6-pyridazone, 3-methyl-6-pyridazone and 6-pyridazone, respectively, identical in each case with authentic samples. This conclusively proves that IIa, IIb and IIc are the dihydropyridazones.



IIa, R = H
b, R = CH_3
c, R = COOEt

IIIa, R = H
b, R = CH_3
c, R = COOEt

IVa, R = H
b, R = CH_3
c, R = COOH

Va, R = H
b, R = CH_3
c, R = H

When compound Ic was similarly treated with bromine it reacted very sluggishly, the bromine being used up only after prolonged refluxing, and from the reaction mixture no homogeneous product could be isolated.

It should be noted here that the compounds Ia, Ib and Ic correspond in properties to those of the compounds previously isolated from these reactions by von Rothenberg,[2] Curtius[3] and Gault,[6] respectively. Thus, previous to this communication only pyrazolones have been isolated from the reaction of α-acylsuccinic esters and hydrazine.

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(1) R. von Rothenberg, *Ber.*, **26**, 2061 (1893).

(2) R. von Rothenberg, *J. prakt. Chem.* [2] **51**, 140 (1895).

(3) T. Curtius, *ibid.*, [2] **50**, 508 (1894).

(4) S. C. De and D. N. Dutt, *J. Indian Chem. Soc.*, **7**, 473 (1930).

(5) A. Sonn, *Ann.*, **518**, 290 (1935).

(6) H. Gault, G. Kalopissis, N. Rist and F. Grumbach, *Bull. soc. chim.*, 916 (1954).

(7) O. Poppenberg, *Ber.*, **34**, 3257 (1901); W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 239 (1947).

Repetition of the reaction of De and Dutt[4] of semicarbazide with diethyl α-acetylsuccinate gave only a compound, melting at 115–116°, that gave correct analyses for the semicarbazone of the starting material.

In order to further characterize our compounds and possibly to provide a means for differentiating between pyrazolones and dihydropyridazones, we have determined the ultraviolet absorption spectrum of each of these substances in 95% ethanol. It will be noted that the only appreciable difference in the spectra of the pyrazolones and the dihydropyridazones is the considerably more intense absorption of the latter.

We are indebted to Mr. Kenneth Kun for the measurement of the ultraviolet spectra.

Experimental[8,9]

Reaction of Diethyl Formylsuccinate with Hydrazine.—A solution of hydrazine hydrate (5.0 g., 0.10 mole) in 100 ml. of water was added slowly with stirring to a solution of diethyl formylsuccinate (20.2 g., 0.10 mole) in 100 ml. of ethanol. The reaction was immediate and the mixture warmed to 45°. When the mixture was chilled there were obtained 8.0 g. (47% yield) of crystals Ia that melted at 167–168.5°. Recrystallization from 95% ethanol did not raise this melting point; ultraviolet absorption[10]: $\lambda_{\max}$ 254 mμ, ϵ 3550; $\lambda_{\max}$ 227 mμ, ϵ 4250.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.47. Found: C, 49.34; H, 5.86; N, 16.54.

The filtrate from the above crystals was evaporated to dryness under vacuum and the residue was boiled out with benzene to ensure dryness; the residue was then shaken with 100 ml. of benzene and this mixture was filtered, yielding an additional 1.5 g. (9%, 56% total yield) of the pyrazolone melting at 161–162°. The benzene filtrate was evaporated to dryness under vacuum and the residue was distilled, giving 1.5 g. (9%) of material boiling at 125–130° (0.4 mm.) (IIa).

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92. Found: C, 50.03; H, 6.52.

In a larger run there was obtained from 10.5 g. of a corresponding distillate 2.0 g. of crystalline material melting at 112–124°. This material, after successive crystallizations from benzene and water, melted at 127–128°, undepressed with a sample of IIIa prepared as described below.

Reaction of Diethyl Acetylsuccinate with Hydrazine.—A solution of hydrazine hydrate (15.0 g., 0.30 mole) in 100 ml. of water was mixed with a solution of diethyl acetylsuccinate (75.6 g., 0.35 mole) in 200 ml. of ethanol. The mixture warmed spontaneously and was then heated at 80° for a few minutes, after which the solution was evaporated to dryness under vacuum. The residue was boiled with 500 ml. of benzene and, when this mixture was chilled, there was obtained 29.0 g. (52.5% yield) of crystals, melting at 156.5–162°, which after recrystallization from ethanol melted at 166–167° (Ib); ultraviolet absorption: $\lambda_{\max}$ 250 mμ, ϵ 4380; inflection at 230 mμ.

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 51.98; H, 6.78; N, 15.39.

The benzene filtrate was evaporated to dryness under vacuum, leaving a partially crystalline mass which was crystallized from 100 ml. of 1:1 benzene–Skellysolve C. There was obtained 11.5 g. (21% yield) of crystals melting at 76–87°; this material, after two recrystallizations from the same solvent mixture, melted at 91.5–92.5° and weighed 4.0 g. (IIb); ultraviolet absorption: $\lambda_{\max}$ 266 mμ, ϵ 6700.

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.16; H, 6.66; N, 14.93.

Reaction of Triethyl Oxalylsuccinate with Hydrazine.—A solution of hydrazine hydrate (10 g., 0.20 mole) in 100 ml. of ethanol was mixed with a solution of triethyl oxalylsuccinate (54.8 g., 0.20 mole) in 100 ml. of ethanol. The mixture warmed spontaneously and was then evaporated to dryness under vacuum. The residue was crystallized three times from ethyl acetate, giving 5.5 g. (11% yield) of material melting at 156–159° (Ic); ultraviolet absorption: $\lambda_{\max}$ 268 mμ, ϵ 5630; $\lambda_{\max}$ 231 mμ, ϵ 10900.

Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.44; H, 5.92; N, 11.54.

The first ethyl acetate mother liquor was evaporated to dryness under vacuum, leaving 35 g. of oily material that was distilled to give 13.5 g. of distillate boiling at 175–180° (0.4 mm.); after four crystallizations from ethyl acetate this furnished 4.8 g. (10% yield) of crystalline material melting at 98–100.5° (IIc); ultraviolet absorption: $\lambda_{\max}$ 269 mμ, ϵ 11300.

Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.55; H, 5.71; N, 11.66.

4-Carbethoxy-6-pyridazone (IIIa).—A solution of 4-carbethoxy-4,5-dihydro-6-pyridazone (IIa) (1.7 g., 0.01 mole) in 10 ml. of glacial acetic acid was heated to boiling and bromine (1.6 g., 0.01 mole) was added. The bromine was consumed immediately and hydrogen bromide was given off. The solution was diluted with 10 ml. of water and then evaporated to dryness under vacuum. The residue, after three crystallizations from water, weighed 1.1 g. (65% yield) and melted at 126.5–127.5°; ultraviolet absorption: $\lambda_{\max}$ 312 mμ, ϵ 2480.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.01; H, 4.79; N, 16.67. Found: C, 50.02; H, 4.80; N, 16.59.

3-Methyl-4-carbethoxy-6-pyridazone (IIIb).—3-Methyl-4-carbethoxy-4,5-dihydro-6-pyridazone (IIb) was treated with bromine as above, yielding the pyridazone melting at 114.5–116°; ultraviolet absorption: $\lambda_{\max}$ 312 mμ, ϵ 2300.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.52; H, 5.65; N, 15.57.

3,4-Dicarbethoxy-6-pyridazone (IIIc).—3,4-Dicarbethoxy-4,5-dihydro-6-pyridazone (IIc), similarly treated with bromine, gave the pyridazone melting at 85.5–87.5°; ultraviolet absorption: $\lambda_{\max}$ 249 mμ, ϵ 7190; inflection at 291 mμ.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.89; H, 4.98; N, 11.71.

4-Carboxy-6-pyridazone (IVa).—4-Carbethoxy-6-pyridazone (IIIa) (0.5 g., 0.003 mole) was heated for one hour at reflux with 5 ml. of 20% hydrochloric acid. At first everything dissolved but soon crystals started to form; the cooled mixture yielded material which, after recrystallization from water, weighed 0.2 g. (*ca.* 50% yield) and melted at 303° dec.; ultraviolet absorption: $\lambda_{\max}$ 303 mμ, ϵ 2350.

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.86; H, 2.88; N, 20.01. Found: C, 42.65; H, 3.09; N, 20.25.

3-Methyl-4-carboxy-6-pyridazone (IVb).—3-Methyl-4-carbethoxy-6-pyridazone (IIIb), by a similar hydrolysis, gave the acid melting at 247° dec.; ultraviolet absorption $\lambda_{\max}$ 301 mμ, ϵ 2310.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.93; N, 18.18. Found: C, 46.89; H, 3.85; N, 17.94.

3,4-Dicarboxy-6-pyridazone (IVc).—3,4-Dicarbethoxy-6-pyridazone (IIIc) by a similar hydrolysis gave a diacid that had undergone partial decarboxylation and which melted at 291° dec.

Anal. Calcd. for $C_6H_4N_2O_5$: C, 39.14; H, 2.19; neut. equiv., 92. Found: C, 41.48; H, 3.68; neut. equiv., 120.

Decarboxylation of IVa, IVb and IVc.—A sample of each of these acids, separately, was mixed with a small amount of copper powder and the mixtures were heated over a free flame in a small flask equipped with a small distilling head and condenser. After the initial bubbling had ceased the heat was raised so as to distil the material slowly. A crystalline distillate was obtained in each case and this was then recrystallized from Skellysolve B.

The products from IVa and IVc each melted at 97–100°, undepressed when mixed with an authentic sample of 6-pyridazone.[11] The product from IVb melted at 138–140°,

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[8] Boiling points and melting points are uncorrected.

[9] Microanalyses were carried out by Miss Lorelinde Einstein.

[10] Ultraviolet absorption data on all compounds were determined in 95% ethanol on a Beckman model DK recording spectrophotometer. For comparative purposes the ultraviolet absorption of 3-methyl-5-pyrazolone was determined: $\lambda_{\max}$ 245 mμ, ϵ 3200.

[11] S. Gabriel, *Ber.*, **42**, 654 (1909).

undepressed when mixed with an authentic sample of 3-methyl-6-pyridazone.[7]

Reaction of Diethyl Acetylsuccinate with Semicarbazide.—A solution of semicarbazide hydrochloride (11.2 g., 0.1 mole) and hydrated sodium acetate (13.6 g., 0.1 mole) in 100 ml. of water was mixed with a solution of diethyl acetylsuccinate (25.6 g., 0.1 mole) in 100 ml. of ethanol. There was no heat evolved on mixing and the mixture was then heated at reflux for one hour, after which the solvents were removed under vacuum. The residue was crystallized from 300 ml. of water to give 16 g. (59% yield) of material melting at 115–116°. Recrystallization did not raise this melting point.

Anal. Calcd. for $C_{11}H_{19}N_3O_5$: C, 48.35; H, 6.97; N, 15.38. Found: C, 48.69; H, 7.13; N, 15.64.

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NOTES

Reduction of Organic Compounds by Lithium in Low Molecular Weight Amines. II. Stereochemistry. Chemical Reduction of an Isolated Non-terminal Double Bond

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It was demonstrated in a previous publication[1] from this Laboratory that lithium, dissolved in methyl, ethyl- and *n*-propylamine, constitutes a powerful reducing medium for aromatic hydrocarbons. In every case thus far investigated this reagent has been found to effect far more extensive reductions than had previously been noted with sodium in liquid ammonia.[2]

It had been established conclusively by Campbell[3] that reduction of acetylenes by sodium in liquid ammonia involved a *trans* addition of hydrogen. Reductions carried out in the lithium–amine system were so markedly different from those effected by sodium in ammonia that it was deemed expedient to determine the stereochemistry of this new reducing medium. An approach similar to that employed by Campbell was utilized successfully in the present study.

When samples of 3-octyne and 5-decyne were reduced at −78° by lithium dissolved in ethylamine, good yields of *trans*-3-octene and *trans*-5-decene were obtained. The configuration of the products was established by comparing their freezing points and infrared spectra with authentic samples of both *cis*- and *trans*-3-octene and 5-decene. These were prepared either by catalytic hydrogenation of the corresponding acetylenes (*cis* product), or by reducing these acetylenes with sodium in liquid ammonia (*trans* product).

During the course of reducing 5-decyne at +17° it was observed that appreciable quantities of *n*-decane were obtained, particularly if lithium in large excess of two equivalents was employed. This was in sharp contrast to the same reduction by sodium in liquid ammonia which stopped cleanly at the olefin stage. Obviously the lithium–amine reagent is capable of reducing a non-terminal unsaturated center. To our knowledge this is the first instance of a chemical reduction not involving a terminal double bond.[4]

This reduction was extended to the olefin series where it was found that cyclohexene could be reduced to cyclohexane, and 1-ethylcyclohexene to ethylcyclohexane.

It obviously could be argued that the reductions observed in the above instances were not actually chemical in nature but rather were brought about by the hydrogen produced from the reaction of lithium with the solvent. Admittedly the latter reaction is much more pronounced with amine solvents than with ammonia. To test this possibility, the quantity of lithium absorbed per mole of cyclohexene reduced was determined. The average uptake of metal in three such determinations was 1.8 gram atoms per mole of cyclohexene. This indicated that reduction of the olefin was proceeding by some type of chemical addition of metal. Such an addition requires two equivalents of metal per equivalent of olefin. If the reduction was being effected simply by hydrogen generated from reaction of lithium with solvent, no constant ratio of metal to olefin would exist.

Experimental

Preparation of 3-Octyne and 5-Decyne.—Reaction of 1-hexyne (b.p. 71°, $n^{20}D$ 1.3989) with sodium amide in liquid ammonia and subsequently with butyl bromide gave a 70% yield of 5-decyne,[3] b.p. 176° at 748 mm., $n^{25}D$ 1.4311. When ethyl bromide was used in the reaction sequence, a 50% yield of 3-octyne[3] (b.p. 132° at 751 mm., $n^{20}D$ 1.4258) was obtained.

Reduction of 5-Decyne with Lithium in Ethylamine. A. At −78°.—A Dry Ice–carbon tetrachloride–chloroform slush was placed around a 500-cc. flask which contained a blue solution of 1.73 g. (0.25 g. atom) of lithium in 300 cc. of ethylamine. To the chilled solution was added 13.8 g. (0.1 mole) of 5-decyne over several minutes. The stirred solution turned gray after four hours; nine grams of methanol was then added and the cooling bath was removed after the hydrolysis of the excess lithium was completed. The solvent was permitted to evaporate partially, petroleum ether (b.p. 35–40°) as well as water was added, and the two-phase system was filtered through Celite. The hydrocarbon layer was separated, washed with water and dilute acid, and dried over calcium chloride. The solvent was distilled off and the residue was fractionally distilled with a Vigreux column (6 mm. outside diameter, three feet long) to give 7.8

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(1) R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, THIS JOURNAL, **77**, 3230 (1955).

(2) For excellent reviews on this topic see G. W. Watt, *Chem. Revs.*, **46**, 317 (1949), and A. J. Birch, *Quart. Revs.*, IV, **69**, (1950).

(3) K. N. Campbell and L. T. Eby, THIS JOURNAL, **63**, 216 (1941).

(4) Sodium in the presence of ammonia and methanol has been used to reduce simple terminal olefins. Apparently the reaction fails completely with non-terminal olefins. See T. J. King, *J. Chem. Soc.*, 898 (1951), and H. Greenfield, R. A. Friedel and M. Orchin, THIS JOURNAL, **76**, 1258 (1954).