The Reaction of Ethyl β-Diazopropionate with Cyclic Ketones

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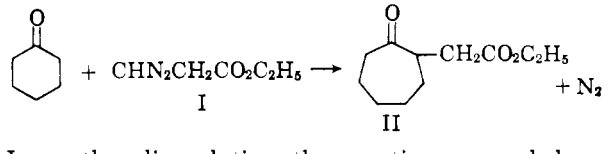
Cyclohexanone and cycloheptanone have been treated with ethyl β-diazopropionate prepared in situ to yield ethyl 2-ketocycloheptylacetate and ethyl 2-ketocyclooctylacetate respectively. Attempts to prepare higher molecular weight esters of β-diazopropionic acid from the corresponding nitrosourethanes are also described.

WHEN ethyl and benzyl β-diazopropionates are prepared, both by in situ and ex situ methods, they undergo the typical reactions of diazoalkanes on treatment with phenolic and enolic compounds (*1*). The present paper describes the reaction of ethyl β-diazopropionate with cyclohexanone and cycloheptanone and some attempts to prepare β-diazopropionic acid esters of higher molecular weight.

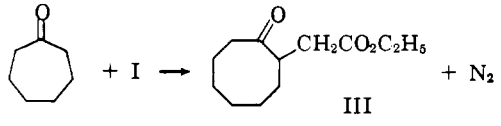
When ethyl β-diazopropionate (I) was prepared ex situ from ethyl *N*-carbethoxy-*N*-nitroso-β-aminopropionate and added to a methanolic or ethanolic solution of cyclohexanone, there was no evidence of a reaction and, on distillation of the resulting mixture, none of the expected ethyl 2-ketocycloheptylacetate (II) was obtained. However, in situ preparation of the diazo ester (I) in ice-cooled alkaline ethanolic solution in the presence of cyclohexanone resulted in a rapid evolution of nitrogen gas and a rise in temperature. By distillation of the reaction mixture II was isolated in 54.5% yield.



In methanolic solution the reaction proceeded more rapidly as indicated by the greater rise in temperature and more copious gas evolution. The yield of II, however, was lower (46.6%).

Ethyl 2-ketocycloheptylacetate (II) has been prepared previously only through a series of reactions involving 2-carbethoxycycloheptanone as the starting material (*4*). Our procedure is an alternate and, seemingly, more convenient method of preparation.

The method has also been extended to the preparation of ethyl 2-ketocyclooctylacetate (III) by treating cycloheptanone with I (prepared in situ) in an ice-cooled solution.



This reaction appeared to proceed much more slowly than the corresponding reaction with cyclohexanone. Only a five degree rise in temperature and a slow evolution of nitrogen gas could be observed. The yield of crude III was 23.3%. A more vigorous nitrogen evolution and a much greater rise in temperature was observed when the reaction was initiated at room temperature and run with no external cooling. However, the reaction run under these conditions produced a mixture of products very difficult to purify. Distillation fractions of approximately the same boiling point as the pure product (obtained from an ice-cooled run) were of considerably lower purity as shown by elemental analysis and refractive index. That a *p*-nitrophenylhydrazone of III was formed on treatment with *p*-nitrophenylhydrazine indicated that III was present in these fractions.

Attempts were also made to prepare higher molecular weight esters of β-diazopropionic acid. In Table I are presented the *N*-carbethoxy-β-aminopropionic acid esters which were prepared for the purpose of eventual conversion to the corresponding diazo compounds: *p*-nitrobenzyl *N*-carbethoxy-β-aminopropionate (IV), *p*-bromophenacyl *N*-carbethoxy-β-aminopropionate (V), and β-naphthyl *N*-carbethoxy-β-aminopropionate (VI). The attempt to prepare the diphenylmethyl ester is described in the experimental portion of this paper.

Conversion of IV and V to the corresponding *N*-nitrosourethanes (VII and VIII, respectively), the necessary precursors for β-diazopropionic acid esters, was successful, while nitrosation of VI failed. Yield data and properties of VII and VIII are also presented in Table I. Attempts to convert the nitrosourethanes to the corresponding diazo esters by the ex situ method used for the preparation of the ethyl and benzyl esters (*1*), were unsuccessful. Also (in contrast to the reactions of the ethyl ester), when *p*-nitrobenzyl *N*-carbethoxy-*N*-nitroso-β-aminopropionate (VII) was treated with base in an ethanolic solution in the presence of cyclohexanone, only the hydrolysis product, *p*-nitrobenzyl alcohol, was obtained. Further examination of the products of the reaction gave no indication that an in situ conversion to a β-diazo ester and a subsequent ring expansion had occurred before hydrolysis of the ester. Likewise, *p*-bromophenacyl *N*-carbethoxy-*N*-nitroso-β-aminopropionate (VIII) yielded no cycloheptanone derivative.

Decomposition of the *p*-bromophenacyl ester to the corresponding diazo ester raises the possibility of an internal reaction between the diazo group and the keto group to yield cyclic compounds. An examination of the products of this reaction revealed no cyclization products, however.

EXPERIMENTAL

Ethyl 2-Ketocycloheptylacetate (II). A 10 gram (0.053 mole) quantity of ethyl *N*-carbethoxy-β-aminopropionate was converted to the corresponding nitroso compound by the procedure of Braun and Looker (*1*). The resulting ether solution was dried over $MgSO_4$ and the solvent was removed and replaced with 85 ml. of absolute ethanol. Cyclohexanone (7.7 grams, 0.071 moles) was added. The solution was ice-cooled and stirred as one pellet of sodium hydroxide was added. The solution turned yellow as a gas evolved and the temperature rose to 30°. After 45 minutes, the mixture was decanted from the remaining alkali and neutralized with concentrated hydrochloric acid. The solvent was removed in vacuo and the remaining oil was distilled through a 3½ × ⅜ inch Vigreux column. The product was collected at 148–150°/ 15 mm. Hg, n_D^{18} 1.4631

Table I. Esters of Acids

Ester	Yield, %	M.P.[a] °C.	Formula	%, Carbon Calcd.	%, Carbon Found	%, Hydrogen Calcd.	%, Hydrogen Found	%, Nitrogen Calcd.	%, Nitrogen Found
N-Carbethoxy-β-aminopropionic									
IV	65	56–58	$C_{13}H_{16}N_2O_6$	52.70	52.65	5.44	5.44	9.46	9.92
V	70	95–96	$C_{14}H_{16}BrNO_5$	46.94	46.93	4.50	4.51	3.91	3.72
VI	44	91–93.5	$C_{16}H_{17}NO_4$	66.88	66.72	5.97	6.09	4.88	5.06
N-Carbethoxy-*N*-nitroso-β-aminopropionic									
VII	87	57–59	$C_{13}H_{15}N_3O_7$	48.00	48.40	4.65	4.78	12.92	12.89
VIII	75	58–60	$C_{14}H_{15}BrN_2O_6$	43.43	43.59	3.90	4.07	7.24	7.37

[a] Uncorrected.

(5.7 grams, 54.5%) and gave a *p*-nitrophenylhydrazone melting at 165–167°. The literature (*4*) gives a b.p. of 140–143°/12 mm. Hg, $n_D^{15.5}$ 1.4664 and a m.p. for the *p*-nitrophenylhydrazone of 168°. All melting points in this report are uncorrected.

Ethyl 2-Ketocyclooctylacetate (III). This compound was prepared in the same manner as II. The reaction of ethyl β-diazopropionate (prepared from 15 grams, 0.08 mole of ethyl *N*-carbethoxy-β-aminopropionate) with cycloheptanone (15.7 grams, 0.14 mole) was much slower, however, and the temperature rose only to a maximum of 7°. After three hours of stirring and cooling followed by another 2 to 3 hours of ice-cooling the mixture was allowed to reach room temperature. After neutralization and removal of the solvent, the remaining oil was distilled through a 3½ × ⅜ inch Vigreux column. Five fractions were collected at 14 mm. Hg.

(a) 9.4 grams, b.p. 25–69°, n_D^{18} 1.4542.
(b) 1.7 grams, b.p. 69–158°, n_D^{18} 1.4582.
(c) 1.7 grams, b.p. 158–161°, n_D^{18} 1.4648.
(d) 4.0 grams, b.p. 161–163°, n_D^{18} 1.4679.
(e) 0.7 grams, b.p. 163°, n_D^{18} 1.4651.

Fraction *d* represented a 23.3% yield of crude product. A 0.3 gram sample yielded a *p*-nitrophenylhydrazone, m.p. 160–165°. The remainder of fraction *d* was redistilled on a 24 inch Podbielniak column to yield three fractions: (*d*-1) 0.6 gram, b.p. 97–168°/19 mm. Hg, n_D^{18} 1.4592; (*d*-2) 1.5 gram, b.p. 168°/19 mm. Hg, n_D^{18} 1.4691; (*d*-3) 1.1 gram, b.p. 168–177°/19–29 mm. Hg, n_D^{18} 1.4700. Fractions *d*-2 and *d*-3 represent a 15.4% yield of pure product. Fraction *d*-2 was analyzed.

ANAL. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.46. Found: C, 67.74; H, 9.40.

Fractions *d*-2 and *d*-3 each gave a *p*-nitrophenylhydrazone. An analytically pure sample of the *p*-nitrophenylhydrazone of III prepared from a similar run melted at 162.5–165.5°.

ANAL. Calcd. for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 61.99; H, 7.25; N, 12.38.

When the reaction was initiated at room temperature and no external cooling was applied, a much more rapid evolution of nitrogen occurred and the temperature rose to 50°. Distillation of the product resulted in fractions with similar boiling points to those described above. They contained III of lesser purity, however, as determined by elemental analysis and refractive index. A fraction (from a 24 inch Podbielniak column) boiling at 160–163°/15 mm., of Hg, n_D^{18} 1.4642, for example, had an elemental analysis of : C, 64.20; H, 8.93. A *p*-nitrophenylhydrazone (m.p. and mixed m.p. with an authentic sample, 160–165°) of III was readily obtained, however, by treatment with *p*-nitrophenylhydrazine.

***p*-Nitrobenzyl *N*-Carbethoxy-β-aminopropionate (IV).** This compound was prepared according to the general directions for the preparation of *p*-nitrobenzyl esters given by McElvain (*3*). From 12.9 grams (0.08 mole) of *N*-carbethoxy-β-aminopropionic acid (*1*) and 16.3 grams (0.08 mole) of *p*-nitrobenzyl bromide was obtained, after one recrystallization from 95% ethanol, 15.4 grams (65.0% yield) of crystals melting at 50–57°. Analytically pure crystals melted at 56–58°.

***p*-Nitrobenzyl *N*-Carbethoxy-*N*-nitroso-β-aminopropionate (VII).** A 2.0 gram (0.068 mole) quantity of IV was dissolved in an ice-cooled solution of eight ml. of water and four ml. of concentrated sulfuric acid. A solution of 1.4 grams of sodium nitrite in two ml. of water was added dropwise with stirring. A solid formed during this reaction. The residue was washed with cold water and recrystallized from 95% ethanol. The yield was 1.9 grams (87.1%) of crystals melting at 53–57°. An analytically pure sample prepared from a similar run melted at 57–59°. The compound appeared to be light sensitive, changing color on exposure.

When 6.3 grams of VII was dissolved in 600 ml. of absolute ethanol in the presence of 4.7 grams of cyclohexanone and a pellet of sodium hydroxide was added, no gas evolution could be detected. Then the mixture was neutralized and the solvent was removed only *p*-nitrobenzyl alcohol was recovered by recrystallization.

Likewise, when an alcohol solution of VII (1.2 grams) was treated with a pellet of sodium hydroxide for several minutes and then, after decantation from the remaining base, benzoic acid (2.0 grams) was added (a procedural modification adopted from Samour and Mason) (*5*), the only products which were recovered were *p*-nitrobenzyl alcohol and benzoic acid.

***p*-Bromophenacyl *N*-Carbethoxy-β-aminopropionate (V).** This compound was prepared in the same manner as the corresponding *p*-nitrobenzyl ester. From 4.8 grams (0.03 mole) of *N*-carbethoxy-β-aminopropionate and 8.4 grams (0.03 mole) of *p*-bromophenacyl bromide the product was obtained without recrystallization, 7.5 grams (70%) of solid, m.p. 95–96°. An analytical sample was prepared from a similar run.

***p*-Bromophenacyl *N*-Carbethoxy-*N*-nitroso-β-aminopropionate (VIII).** This compound was prepared in the same manner as the corresponding *p*-nitrobenzyl ester. Nitrosation of 7.5 grams (0.02 mole) of V yielded 5.7 grams (75%) of needlelike crystals melting at 56–60° after one recrystallization from 95% ethanol. An analytical sample prepared from a similar run melted at 58–60°.

This compound (VIII) showed no evidence of conversion to the corresponding diazo compound when dissolved in absolute ethanol and treated with a sodium hydroxide pellet. The addition of benzoic acid (*5*) to the decanted solution yielded no benzoate as a derivative.

An ethanolic solution of VIII was treated with solid sodium hydroxide, allowed to stand for a few hours, and neutralized. The only material that was obtained from this mixture was *p*-bromobenzoic acid, a probable oxidation product of *p*-bromophenacyl alcohol, resulting from the hydrolysis of VIII.

β-Naphthyl *N*-Carbethoxy-β-aminopropionate (VI). An 8

gram (0.05 mole) quantity of *N*-carbethoxy-β-aminopropionic acid was dissilved in 15 ml. of thionyl chloride. The mixture was allowed to stand with occasional ice-bath cooling when gas evolution became too rapid. After a short time gas evolution ceased and the mixture was allowed to stand overnight at room temperature. The excess thionyl chloride was removed under reduced pressure and a solution of 7.3 grams (0.05 mole) of β-naphthol in 175 ml. of benzene was added. Pyridine (10 ml.) was added and a white ppt. formed, which was removed by filtration. The filtrate was extracted with 5% HCl, 5% $NaHCO_3$, 1% NaOH, and, finally, with water. It was dried over $MgSO_4$, and the solvent was removed in vacuo. The remaining solid was recrystallized first from 95% ethanol and then from benzene-petroluem ether. Recovered were 6.2 grams (44%) of crystals melting at 91.5–93°. An analytical sample was prepared from a similar run, m.p. 91–93.5°.

On dissolving the β-naphthyl ester in aqueous sulfuric acid and treating with sodium nitrite, no product separated. When the addition was complete and the reaction mixture was diluted with water, only a tarry mass separated from which no crystalline product was obtained by any means attempted.

Attempted Preparation of Diphenylmethyl *N*-Carbethoxy-β-aminopropionate. The preparation of this ester was attempted by means of treating diphenylmethyl bromide with *N*-carbethoxy-β-aminopropionic acid in the presence of alkali (*3*). A thick oil was obtained which was resistant to crystallization.

When this oil was treated with sulfuric acid preliminary to nitrosation, solid benzhydryl ether was formed, as shown by mixed m.p. with an authentic sample. The formation of this ether is not surprising in view of its ready formation from diphenylmethyl bromide in water (*2*).

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The Swamping Catalyst Effect VII. Synthesis of 1,6-Diacetonaphthalene

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MANY ATTEMPTS were made in this Laboratory to acylate acetophenone under swamping conditions. They, like previous attempts (*1*), failed, and it was concluded that the acylating agent was not active enough to substitute into a deactivated nucleus. Even trifluoroacetyl chloride failed to substitute into acetophenone but instead was converted to carbon. Apparently, acetophenones cannot be acylated except if an alkyl group is situated ortho to the acetyl group such as in acetomesitylene (*4*).

Although diacylation of a benzene ring was not possible, diacylation of a naphthalene ring was brought about by acetylation of β-acetonaphthalene to yield the new compound, 1,6-diacetonaphthalene. Characterization of this compound is given in the Experimental and described more fully in the thesis by McIntosh (*6*).

EXPERIMENTAL

1,6-Diacetonaphthalene. The apparatus, conditions and isolation have been described (*8*). β-Acetonaphthalene (85 grams, 0.5 mole) was complexed with anhydrous aluminum chloride (1.6 mole) while the internal temperature was maintained at 70–80°. The complex was a viscous, reddish black fluid. Acetyl chloride (0.66 mole) was added dropwise to the stirred mixture over a period of about an hour and the mixture heated at 70–80° for an additional hour. The crude product, b.p. 147–160° at 0.1 mm. Hg, weighed 82 grams, 77%, m.p. 65–70°. It was recrystallized from a mixture of methylcyclohexane and isopropyl alcohol to give 53 grams (50%) of slightly off white fine crystals, m.p. 80.8–82°. A small sample, sublimed at 0.1 mm. Hg, melted at 82–82.5°.

Calcd. for $C_{14}H_{12}O_2$: C, 79.23: H, 5.70. Found: C, 79.13; H, 5.85.

1,6-Dicarboxynaphthalene. The diketone was oxidized with aqueous sodium hypobromite using a Morton high speed stirrer to give intimate contact between diketone and reagent (*7*). The diacid was obtained in 76% yield, m.p. 322–325°, reported m.p. 310° (*2*); neutral equivalent calcd. 108, found 108.8; dimethyl ester made from the acid chloride and methanol, m.p. 97.5–98°, reported 99° (*2*).

1,6-Diacetaminonaphthalene. The dioxime, m.p. 189–191°, made from the diketone, was rearranged to the titled compound by the method of Horning (*5*). The yield was 80% of white needles, m.p. 262.5–263.5°, reported m.p. 263.5° (*3*).

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