t-Boc-L-val-P-ala-OMe, 15136-15-9; *t*-Boc-L-pro-L-leu-OMe, 15136-16-0; *t*-Boc-L-pro-D-leu-OMe, 15136-17-1; *t*-Boc-L-thr-E-cbz-L-eys-OBz, 15180-24-2; cyclo-L-phe-L-phe, 5,254-61-5; cyclo-L-phe-D-phe, 15136-18-2; cyclo-L-phe-L-ala, 15180-22-0; cyclo-L-phe-D-ala, 15136-19-3; cyclo-L-leu-L-phe, 7280-77-5; cyclo-L-leu-D-phe, 13620-18-3; cyclo-L-leu-L-leu, 952-45-4; cyclo-L-leu-D-leu, 15136-23-9; cyclo-L-val-L-leu, 15136-24-0; cyclo-L-val-D-leu, 15136-25-1; cyclo-L-val-L-ala, 15136-26-2; cyclo-L-val-D-ala, 15136-27-3; cyclo-L-leu-L-pro, 2873-36-1; cyclo-L-thr-ε-cbz-L-lys, 15180-23-1; cyclo-L-leu-L-try, 15136-34-2; cyclo-gly-L-phe, 10125-07-2.

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Di(cyclopropanecarbonyl)furoxan[1]

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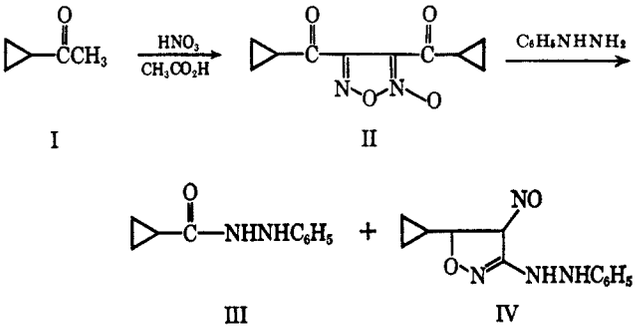
The conversion of aromatic methyl ketones by a mixture of nitric and glacial acetic acids into diaroylfuroxans has been reported.[2] In similar studies with thiophene derivatives, bis(3-thianaphthenoyl)furoxan[3] and di(2-thenoyl)furoxan[4] have been prepared. Dipicolinoyl- and di(6-acetylpicolinoyl)furoxans[5] have been isolated in studies of pyridine derivatives.

We have now been successful in extending this reaction to methyl cyclopropyl ketone, thus broadening the scope of a well-known reaction and lending hope for the synthesis of other alicyclic and possibly aliphatic substituted furoxans. Di(cyclopropanecarbonyl)furoxan (II) was isolated in 45% yield as a pale yellow liquid, bp 63–64° (0.005 mm). The infrared spectra has bands characteristic of furoxan.[6] The nmr spectra indicated that the cyclopropane ring remains unchanged (δ 1.35, methylene protons; δ 2.65, methine protons, areas ratio of 4:1). However, attempts made to distil at higher temperature only result with decomposition and polymerization.

Further transformations have confirmed the furoxan structure. On treatment with phenylhydrazine, the yellow liquid II is transformed into a colorless benzoyl β-phenylhydrazine and yellow 3(β-phenylhydrazino)-4-nitroso-5-phenylisoxazole.[7] One of the two isolated products has been established as cyclopropanecarboxylic acid 2-phenylhydrazide (III) on the basis of the melting point of an admixture with an authentic sample which was prepared by the reaction of ethyl cyclopropylcarboxylate with phenylhydrazine. By analogy, the other product is assigned the structure of 3-(β-phenylhydrazino)-4-nitroso-5-cyclopropylisoxazole (IV) (Scheme I).

SCHEME I



Treatment of II with a 1:1 ratio of 2,4-dinitrophenylhydrazine in methanol gave the mono-2,4-dinitrophenylhydrazone derivative; a 1:2 ratio of II and 2,4-dinitrophenylhydrazine in ethanol gave the bis(2,4-dinitrophenylhydrazone).

Alkaline hydrolysis of compound II resulted in nearly quantitative transformation of 1 mole of the furoxan to 2 moles of cyclopropanecarboxylic acid which was identified by conversion into the corresponding amide.

Experimental Section[8]

Di(cyclopropanecarbonyl)furoxan (II).—To 8.4 g (0.1 mole) of cyclopropyl methyl ketone in 10 ml of glacial acetic acid at 50–55° (external heating with a water bath) was added with stirring in one portion 13 ml of 69% nitric acid (*d* 1.42) dissolved in 10 ml of glacial acetic acid. Immediately, 0.2 g of sodium nitrite was added. Stirring was continued until the temperature reached 80°; then the water bath was removed. After the exothermic reaction subsided, the reaction mixture was then added to 250 ml of ice water which caused an oil to separate. After extraction with three portions of 150 ml of ether, the combined ether extracts were washed with a small amount of cold water, then washed with 5% sodium carbonate solution until the aqueous phase was yellow. Finally, the ether fraction was washed again with cold water and dried over anhydrous sodium sulfate. Evaporation of the ether to dryness under vacuum gave a yellow oil which was heated at 50–55° for 96 hr under 0.1-mm pressure to remove starting materials and volatile impurities. Yellow oil (5 g, 45%) was isolated as crude material. The pure sample was obtained by distillation at 63–64° (0.005 mm), $n^{25}D$ 1.5360.

Anal. Calcd for $C_{10}H_{10}O_4N_2$ (222): C, 54.05; H, 4.54; N, 12.61. Found (osometric in benzene): C, 53.67; H, 4.83; N, 12.51; mol wt, 220.

Infrared absorption (cm^{-1}, neat) was found at 695 s, 720 m, 790 m, 815 m, 870 s, 950 s, 990 s, 1035 s, 1060 s, 1100 s, 1160 m, 1200 s, 1215 w, 1300 s, 1390 s, 1400 s, 1430 s, 1610 s, 1700 s, and 3005 m.

Reaction of Di(cyclopropanecarbonyl)furoxan (II) with Phenylhydrazine.—Compound II (1 g, 0.45 mmole) was suspended in 5 ml of phenylhydrazine in a small flask and shaken until an exothermic reaction began. This was accompanied by evolution of the gas. The flask was allowed to cool slowly to room temperature. The reaction mixture was then poured into a large volume of water. After decanting the water layer, the residue was fractionally crystallized from ethanol to yield two fractions. One fraction of colorless needles, 0.7 g (0.4 mmole, 44%), mp 188–189°, was identified as cyclopropylcarboxylic acid phenylhydrazide (III) by mixture melting point with an authentic sample with no depression.

(1) Presented at the 154th National Meeting of The American Chemical Society, Chicago, Ill., Sept 1967.

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(8) (a) All the melting points and boiling points are uncorrected. (b) The di(cyclopropanecarbonyl)furoxan is particularly irritating and may cause severe rash with certain individuals.

Anal. Calcd for $C_{10}H_{12}ON_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.41; H, 6.60; N, 16.00.

A second fraction was isolated as a yellow solid, yield 0.25 g (0.1 mmole, 22%), mp 100–101° dec, and was identified as 3-(β-phenylhydrazino)-4-nitroso-5-cyclopropylisoxazole (IV): infrared absorption (cm^{-1}, Nujol mull), 950 s, 1010 s, 1030 s, 1310 w, 1360 s, 1600 s, 1625 s, 3040 m.

Anal. Calcd for $C_{12}H_{12}O_2N_4$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.19; H, 5.26; N, 23.12.

Reaction of Di(cyclopropanecarbonyl)furoxan (II) with 2,4-Dinitrophenylhydrazine.—A solution of 0.56 g (0.25 mmole) of II in 10 ml of methanol was heated to boiling while a solution of 0.50 g (0.25 mmole) of 2,4-dinitrophenylhydrazine in 25 ml of methanol was added. Upon addition of a few drops of concentrated HCl, the yellow mono-2,4-dinitrophenylhydrazone derivative was isolated and recrystallized a few times from alcohol: mp 118–119°; yield, 0.81 g (0.2 mmole, 80%).

Anal. Calcd for $C_{15}H_{14}O_7N_6$: C, 47.76; H, 3.51; N, 20.89. Found: C, 47.76; H, 3.50; N, 20.75.

A solution of 0.56 g (0.25 mmole) of II in 10 ml of ethanol was heated to boiling while a solution of 1.0 g (0.50 mmole) of 2,4-dinitrophenylhydrazine in 25 ml of ethanol was added. After addition of a few drops of concentrated HCl, the mixture was heated to reflux for 2 hr. The yellow solid was separated by filtration while the solution was still hot and recrystallized repeatedly from nitromethane: mp 250–251° dec; yield, 0.41 g (0.07 mmole, 28%).

Anal. Calcd for $C_{22}H_{15}O_{10}N_{10}$: C, 45.36; H, 3.12; N, 24.05. Found: C, 45.42; H, 3.53; N, 24.18.

Hydrolysis of II.—A suspension of 1.55 g (0.7 mmole) of di(cyclopropanecarbonyl)furoxan in 20 ml of 10% NaOH solution was heated in a water bath for 2 hr, then evaporated under vacunm to a small volume, acidified with 50% H_2SO_4, and extracted with ether. The combined ether extracts were washed with water and dried with anhydrous sodium sulfate. The major portion of the ether was removed, then replaced by methylene chloride, which was distilled off, followed by fractional distillation under vacuum. The middle fraction which distilled at at 94° (35 mm) was identified as cyclopropane carboxylic acid: yield, 0.5 g (71%) of colorless liquid; $n^{26}D$ 1.4350 (lit.[9] bp 182–184°; $n^{20}D$ 1.4390). This liquid was converted into the corresponding amide by a standard procedure. The colorless solid gave no depression of mixture melting point with authentic cyclopropanecarboxamide, mp 123–125°.

Registry No.—II, 15158-43-7; II bis(2,4-dinitrophenylhydrazone), 15158-44-8; III, 15158-45-9; IV, 15158-46-0.

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Studies on the Synthesis of Extended β-Carbonyl Compounds

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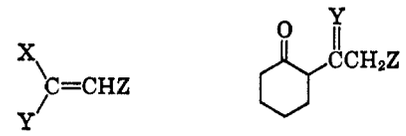
Because of the widespread occurrence of acetate-derived poly-β-carbonyl systems and related species in nature, we were prompted to investigate new approaches to the synthesis of such compounds. Although the terminal acylation of dianions derived from β-diketones has been employed[2] to achieve this end, the required conditions are incompatible with a number of sensitive functional groups. Our aim has therefore been to develop a milder and more selective synthetic method. In this Note we wish to report some successful alkylations of 1-pyrrolidinocyclohexene (I) to generate derivatives of 1,3,5-triketones.

One attractive approach to such systems would be a Michael addition of enamine I to a compound of general formula II, where X is the leaving group, Y represents a function which can be transformed to a carbonyl by hydrolysis and ketonization, and Z is a carbonyl derivative. One simple model with the required functionalization is ethyl-2,2-diethoxyacrylate (IIa).[3] However, reaction of IIa with I followed by work-up with aqueous acid produced cyclohexanone and diethyl malonate as the only detectable neutral products.



IIa, X = Y = OEt; Z = CO_2Et IIIa, Y = NH; Z = CN
b, X = $OPO(OCH_3)_2$; Y = NH_2; Z = CN b, Y = O; Z = CO_2Et

In a more successful attack, the Perkow reaction[4] of 2-bromocyanoacetamide and trimethyl phosphite afforded a compound which is assumed, on the basis of previous research,[5] to have structure IIb. Further reaction of this crude material with I followed by cautious aqueous acid hydrolysis gave a 23% yield of crystalline tricarbonyl derivative IIIa. Variations in the reagent proportions and reaction times failed to increase the yield. The analogous alkylation reaction of the adduct of diethyl bromomalonate[6] and trimethyl phosphite with I was sluggish and required refluxing for 4 hr in benzene for completion, as judged by separation of dimethyl phosphate. The products of hydrolytic work-up were diethyl malonate and cyclohexanone rather than the desired IIIb or its transformation products.

The ketoketenimines (V) derived from base-catalyzed ring opening of suitably substituted isoxazolium salts (IV)[7] suggested themselves as particularly reactive intermediates toward enamine alkylation (Chart I). In a model experiment N-ethyl-5-phenylisoxazolium fluoroborate (IVa) was treated with 1 equiv of triethylamine and an excess of I. Work-up with aqueous acetic acid afforded a 16% yield of the fluoroborate salt of VIIa probably resulting from cyclization of the intermediate VIa or a related species.

Attempts to extend this method with a simple 5-alkoxy isoxazolium salt IVb (seemingly an ideal reagent for the synthesis of β-δ-diketo esters) were frustrated

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