Condensations at the Methyl Group of Benzoylacetone and Acetylacetone with Phthalic Esters by Sodium Amide and Sodium Hydride[1]

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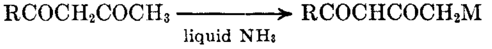
Twofold aroylations at the terminal methyl groups of benzoylacetone and acetylacetone were effected with dimethyl terephthalate by means of sodium amide in liquid ammonia to form corresponding bis-1,3,5-triketones, which are hexaketones. Similar condensations by means of sodium hydride afforded mainly monoaroylation products. One of the hexaketones was cyclized by sulfuric acid to afford the bis-4-pyrone. Diethyl phthalate was condensed with benzoylacetone and acetylacetone by means of sodium hydride to give the corresponding 1,3-indandione derivatives, which are tetraketones. One of these products was independently synthesized by benzoylation of 2-acetyl-1,3-indandione with methyl benzoate by means of sodium hydride. The tetraketones reacted with ethanolic ammonia to form enamines. Conversion of a tetraketone to a trisodium salt and a hexaketone to a hexasodio salt was apparently accomplished by means of sodium amide in liquid ammonia but benzylation of these salts failed. Diethyl phthalate was condensed with a 1,3,5-triketone to produce a pentaketone.

Originally,[2] aroylation at the methyl group of benzoylacetone or acetylacetone (I, R = C_6H_5 or CH_3) to form a 1,3,5-triketone was effected by means of 2 mol equiv of potassium amide in liquid ammonia, which converted the β-diketone to the intermediate dipotassio salt I'' (eq 1, M = K). For example, I was benzoylated with methyl benzoate to form triketone II (eq 2, R = CH_3 or C_6H_5).



$$\underset{\text{I}}{RCOCH_2COCH_3} \xrightarrow[\text{liquid } NH_3]{2MNH_2} \underset{\text{I''}}{RCO\overset{M}{C}HCOCH_2M} \quad (1)$$

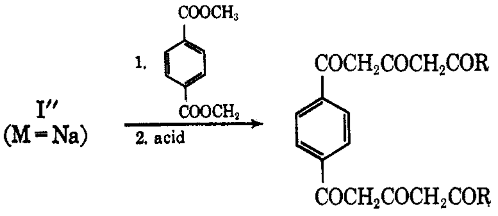
$$I'' \xrightarrow[\text{2. acid}]{\text{1. } C_6H_5COOCH_3} \underset{\text{II}}{RCOCH_2COCH_2COC_6H_5} \quad (2)$$

Because the triketone II is produced in the reaction mixture as its dialkali salt, either 2 mol equiv of the dialkali salt I'' to one of the ester were employed or an extra equivalent of the alkali amide was used. The former procedure, in which one-half of the original β-diketone was regenerated, appeared to be preferable.[2b]

Recently,[3] such terminal aroylations have been accomplished more efficiently by means of excess sodium hydride in refluxing 1,2-dimethoxyethane (monoglyme), even though the dialkali diketone I'' (M = Na) did not appear to be an intermediate.[3]

In the present investigation, a study was made of the possible twofold aroylation at the terminal methyl group of such β-diketones with phthalic esters and of further reactions of certain of the products. This study promised to afford some interesting multiple ketones and cyclic products.

Disodiobenzoylacetone and disodioacetylacetone, prepared by means of sodium amide (see eq 1, M = Na), underwent twofold aroylations with dimethyl terephthalate to form the corresponding bis-1,3,5-triketones, which are hexaketones IIIa and b, respectively (eq 3).



(3)

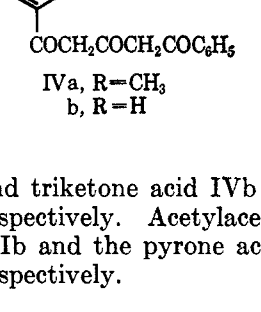
IIIa, R = C_6H_5
b, R = CH_3

Structures IIIa, b were supported by analyses and infrared spectra which showed broad bands characteristic of β-diketones as well as strong absorption characteristic of *para* disubstitution.

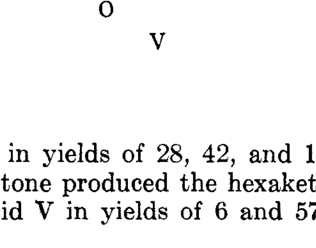
The use of 4 mol equiv of the disodio salt I'' to one of dimethyl terephthalate, which corresponds to that of 2 equiv of I to 1 equiv of methyl benzoate,[2b] afforded hexaketones IIIa and b in yields of 40 and 49%, respectively. In both reactions, terephthalamide was formed as a by-product. For example, in the latter case, 37% of the diamide was isolated.

The use of 2 equiv of disodioacetylacetone to 1 equiv of the phthalic esters in the presence of an extra 2 equiv of sodium amide gave hexaketone IIIb in only 9% yield; the main products were terephthalamide (62%) and apparently another amide that contained a 1,3,5-triketone (or 1,3-diketone) group.

Also, dimethyl terephthalate was condensed with the β-diketones by means of sodium hydride, but most of the reaction was evidently arrested at the monoaroylation stage. Thus, the reaction with benzoylacetone afforded hexaketone IIIa, triketone ester IVa,



IVa, R = CH_3
b, R = H



V

and triketone acid IVb in yields of 28, 42, and 19% respectively. Acetylacetone produced the hexaketone IIIb and the pyrone acid V in yields of 6 and 57%, respectively.

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[1] This investigation was supported by the Petroleum Research Fund administered by the American Chemical Society and by Public Health Service Research Grant CA-04455 from the National Cancer Institute.

[2] (a) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958). (b) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).

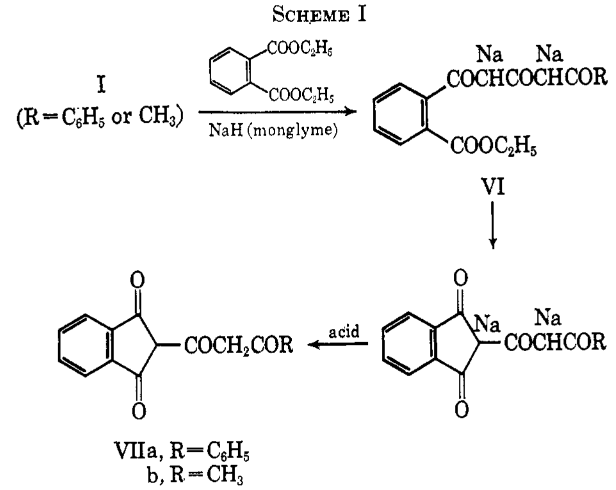
[3] M. L. Miles, T. M. Harris, and C. R. Hauser, *ibid.*, **30**, 1007 (1965).

The triketone acid IVb apparently resulted from reaction of the monoaroylated product IVa[4] rather than from cleavage of the hexaketone IIIa, since a blank experiment with IIIa and sodium hydride failed to produce IVb. The pyrone acid V presumably arose through cyclization of the intermediate triketone acid; although such cyclizations have generally been acid catalyzed,[2b] the present one might have been base catalyzed (see Experimental Section).

The structures of these monoaroylated products were supported by analyses and absorption spectra. The infrared spectra of both triketo ester IVa and triketo acid IVb had broad bands characteristic of β-diketones which were notably absent in the spectrum of the pyrone acid V. The spectrum of IVa showed a peak for the carbonyl of an ester group, and those of IVb and V showed peaks for the carbonyl of a carboxyl group. The ultraviolet spectrum of V exhibited absorption characteristic of a 4-pyrone.

Whereas the terephthalic ester produced intermolecular di- or monoaroylation products of the β-diketones, diethyl phthalate underwent an intermolecular aroylation followed by an intramolecular cyclization to afford 1,3-indandione derivatives, which are tetraketones. Moreover, sodium hydride was more satisfactory than sodium amide for this process. Thus, condensation of benzoylacetone and acetylacetone with the *o*-phthalic ester by means of sodium hydride produced VIIa, b in yields of 51 and 46%, respectively (Scheme I). Presumably, VI was an intermediate that cyclized.

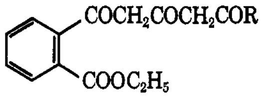
SCHEME I



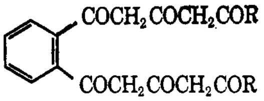
VIIa, R = C_6H_5
b, R = CH_3

The condensation of benzoylacetone with diethyl phthalate to give tetraketone VIIa was also realized by means of sodium amide in liquid ammonia but the yield was only 19%.

That the products were indeed the indandiones VIIa, b, not the possible uncyclized monoaroyl derivatives VIII or the diaroyl derivatives IX, was supported by analysis and infrared spectra which showed only β-diketone type absorption in the carbonyl region in addition to absorption characteristic of *ortho* disubstitution.

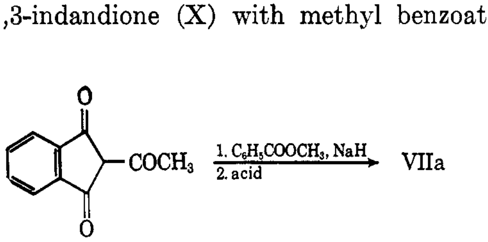


VIII



IX

The indandione structure of VIIa was confirmed by independent synthesis involving benzoylation of 2-acetyl-1,3-indandione (X) with methyl benzoate (eq 4).



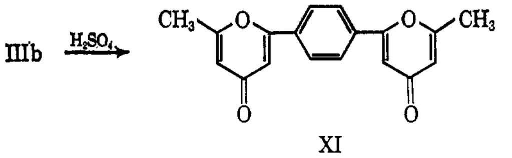
X

(4)

This benzoylation (eq 4) furnishes an alternative route to the synthesis of tetraketone VIIa, the yield of which was 48%. However, the corresponding acetylation of X with ethyl acetate to form VIIb might not be as satisfactory because of possible self-condensation of the ester.

Incidentally, the intramolecular acylation of the dianion intermediate VI to form VIIa, b is analogous to the intramolecular acylations of monoanions that occur in base catalyzed condensations of diethyl phthalate with methyl ketones to form acyl-1,3-indandiones, for example X.[5]

Further Reactions of Products.—Similar to 1,3-triketones II (R = CH_3 or C_6H_5) which have previously been cyclized with cold, concentrated sulfuric acid to form 4-pyrones,[2b] hexaketone IIIb underwent cyclization with this acid to form the bis-4-pyrone XI in 51% yield (eq 5).



XI

(5)

Structure XI was supported by analysis and absorption spectra. Its ultraviolet spectrum was characteristic of a 4-pyrone.[2b] Its infrared spectrum showed a sharp peak characteristic of a doubly conjugated carbonyl group, and no broad band such as that observed in the original 1,3,5-triketone. This observation, together with the analysis, showed that the product was not the possible triketopyrone which would have resulted had only one of the triketone groups undergone cyclization.

Surprisingly, tetraketones VIIa, b, which are also 1,3,5-triketones, failed to afford 4-pyrones with sulfuric acid under similar conditions, and the starting compounds were recovered. Moreover, these compounds failed to undergo cyclization with ethanolic ammonia to form 4-pyridones under conditions that readily convert 1,3,5-triketones II to such products.[2b] However, one of the carbonyl groups of each of the tetraketones VIIa, b reacted with the ammonia to form imines or enamines, presumably XIIa, b or XIIIa, b, in yields of 82 and 80%, respectively. These reactions were as-

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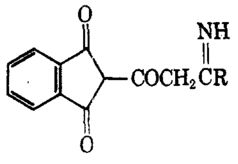
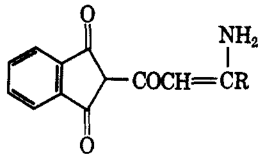
[4] A similar result was obtained with ethyl acetoacetate, ethyl benzoate, and sodium hydride; see J. F. Wolfe, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3249 (1964).

[5] See L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

sumed to involve the terminal carbonyl groups of VIIa, b because this position of VIIb was observed to be attacked by 10% alkali resulting in cleavage to form the acetyl-1,3-indandione X.



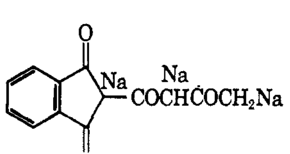
XIIa, R = C_6H_5
b, R = CH_3



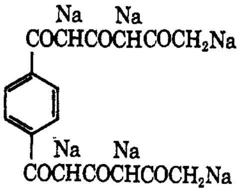
XIIIa, R = C_6H_5
b, R = CH_3

The general structures of the products XIIa, b or XIIIa, b were supported by analyses and absorption spectra. The infrared spectra showed broad bands characteristic of a β-diketone group and strong absorption for a hydroxyl or amino group. Since no absorption for an imine group was observed, the products appeared to be enamines XIIIa, b rather than imines XIIa, b.[6] The ultraviolet spectra did not show absorption characteristic of a 4-pyridone[2b] (see above).

Although tetraketone VIIb and hexaketone IIIb were evidently converted by appropriate amounts of sodium amide in liquid ammonia to the trisodio salt VII'b and hexasodio salt III'b, respectively, these salts failed to undergo appreciable alkylation with benzyl chloride within 1 hr, and VIIb and IIIb were largely recovered. Had an appreciable amount of sodium amide been present in equilibrium, the halide should have undergone self-condensation to form stilbene, a reaction that is accompanied by the production of a purple color[7]. However, none of this hydrocarbon was isolated and this color was not observed. Apparently the polysodio salts VII'b and III'b were too insoluble for benzylation to be realized under the conditions employed. Also an unsuccessful attempt was made to benzoylate tetraketone VIIb by means of sodium hydride.

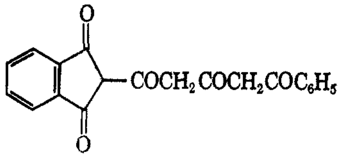


VII'b



III'b

A Related Result.—Triketone II (R = CH_3) was condensed with diethyl phthalate by means of sodium hydride to form the pentaketone XIV in 29% yield.



XIV

Structures XIV was supported by analysis and infrared spectrum which indicated the presence of a β-diketone group as well as *ortho* disubstitution.

Experimental Section

Melting points were taken on a Thomas–Hoover melting point apparatus in open tubes and are uncorrected. Analyses were by Janssen Pharmaceutica, Beerse, Belgium. Infrared spectra were obtained with a Perkin-Elmer Model 237 spectrophotometer using the potassium bromide pellet method. Ultraviolet spectra were determined with a Beckman DB spectrophotometer.

Condensations of β-Diketones I with Dimethyl Terephthalate by Sodium Amide.—To a stirred suspension of sodium amide (0.20 mole) in 300 ml of commercial, anhydrous liquid ammonia[8] was added 16.2 g (0.10 mole) of benzoylacetone in 50 ml of dry ether to form a greenish-brown solution. After 30 min, 4.85 g (0.025 mole) of solid dimethyl terephthalate was added and rinsed in with ammonia. The mixture was stirred for 1 hr, and the ammonia was then evaporated (steam bath). The bright yellow residue was stirred with 250 ml of 10% hydrochloric acid for 30 min. The resulting mixture was filtered, and the solid was shaken with 95% ethanol and again filtered. The remaining solid consisted of 4.48 g (40%) of 1,4-bis(5-phenyl-1,3,5-triketopentyl)benzene (IIIa), mp 179–181°; the melting point was the same after recrystallization from dimethylformamide (DMF). The infrared spectrum showed peaks at 810 (*para* disubstitution),[9] 755 and 690 (monosubstituted phenyl),[9] and a broad band centered at 1600 cm^{-1} with maxima occurring at 1650, 1625, and 1590 cm^{-1} (β-diketone).[9]

Anal. Calcd for $C_{28}H_{22}O_6$: C, 74.00; H, 4.88. Found: C, 74.14; H, 4.81.

Similarly, 10.0 g (0.10 mole) of acetylacetone was condensed with 4.85 g (0.025 mole) of dimethyl terephthalate by 0.20 mole of sodium amide. The reaction mixture was worked up as described above to afford 4.04 g (49%) of 1,4-bis(1,3,5-triketohexyl)benzene (IIIb), mp 185–188°; recrystallization from DMF–ethanol gave a yellow powder, mp 188–190°. The infrared spectrum showed peaks at 820 (*para* disubstitution),[9] 726 (*p*-dicarbonyl substitution),[10] and a broad band centered at 1610 cm^{-1} with maxima at 1700, 1670, and 1590 cm^{-1} (β-diketone).[9]

Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.36; H, 5.24.

Concentration of the original ethanol filtrate precipitated 1.52 g (37%) of terephthalamide, mp 316–320°, identified by comparison of its infrared spectrum with that of an authentic sample.

In another experiment, 5.0 g (0.05 mole) of acetylacetone in 50 ml of dry ether was added, under nitrogen, to a suspension of 0.20 mole of sodium amide in 300 ml of liquid ammonia. After 30 min, 9.7 g (0.05 mole) of solid dimethyl terephthalate was added. The resulting suspension was stirred for 2 hr and worked up as above to give 0.42 g (9%) of IIIb, 2.68 g (62%) of terephthalamide, and 3.16 g of a nitrogen containing material, mp >320°, which could not be purified sufficiently for elemental analysis. The infrared spectrum of the compound showed peaks at 3350 and 3125 (amide)[9] and a broad band at 1600 cm^{-1} (β-diketone).[9]

Condensations of β-Diketones I with Dimethyl Terephthalate by Sodium Hydride.—To a stirred suspension of 6.9 g (0.154 mole) of sodium hydride (56% dispersion in mineral oil)[11] in 50 ml of dimethoxyethane (monoglyme), was added 8.1 g (0.05 mole) of benzoylacetone in 50 ml of monoglyme. The resulting tan suspension was stirred for 30 min; then, 4.85 g (0.025 mole) of solid dimethyl terephthalate was added from a 125-ml erlenmeyer flask through Gooch tubing. The diester remaining in the flask was rinsed in with 100 ml of monoglyme, and the orange suspension was refluxed for 2 hr. The monoglyme was then distilled under reduced pressure, leaving a pasty orange mass to which was added, with stirring, 200 ml of iced water (caution) and 100 ml of ether. The two layers were separated. The aqueous layer was washed with 50 ml of ether and added to a slight excess of

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(6) Similar β-diketone derivatives have been considered to have an enamine rather than an imine structure; see N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.*, **71**, 3337 (1940); S. Boatman and C. R. Hauser, *J. Org. Chem.*, **31**, 1785 (1966).

(7) See C. R. Hauser, W. R. Brasen, P. Skell, J. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **87**, 1653 (1956).

(8) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(9) See L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958.

(10) A. Miyake, *J. Polymer Sci.*, **38**, 506 (1959).

(11) Obtained from Metal Hydrides, Inc., Beverly, Mass.

iced, concentrated hydrochloric acid. The resulting yellow suspension was then made basic by the addition of solid sodium bicarbonate, and the mixture was filtered. The filtrate was neutralized with 12 *N* hydrochloric acid to precipitate 3.31 g (42%) of 4-(5-phenyl-1,3,5-triketopentyl)benzoic acid (IVb), mp 209–211°. Further recrystallization from 95% ethanol gave yellow platelets of IVb, mp 213.5–215°. The infrared spectrum showed peaks at 2590 and 1690 (COOH)[9] and a broad band centered at 1590 cm^{-1} (β-diketone).[9]

Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.54; H, 4.53.

Anal. Calcd: neut equiv, 155.[12] Found: neut equiv, 159.

The solid remaining after filtration of the bicarbonate mixture (see above) was extracted overnight with 95% ethanol in a Soxhlet extractor. Concentration and cooling of the ethanolic extract precipitated 1.6 g (19%) of methyl-4-(5-phenyl-1,3,5-triketopentyl)benzoate (IVa), yellow powder, mp 172–174° (became brown at 154°). The infrared spectrum showed peaks at 1725 (ester)[9] and a broad band centered at 1590 cm^{-1} (β-diketone).[9]

Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98. Found: C, 70.51; H, 4.97.

The solid remaining in the Soxhlet thimble consisted of 3.18 g (28%) of hexaketone IIIa, mp 179–181°, undepressed on admixture with a sample of IIIa prepared by means of sodium amide (see above). Also, the infrared spectra of the two samples were identical.

Similarly, reaction of 5.0 g (0.05 mole) of acetylacetone with 0.154 mole of sodium hydride and 0.25 mole of dimethyl terephthalate yielded 3.18 g (57%) of the sodium bicarbonate soluble solid, 2-methyl-6-(4-carboxyphenyl)-4-pyrone (V), mp 310° dec. The infrared spectrum showed peaks at 3000 and 1700 (COOH)[9] and at 1650 cm^{-1} (pyrone).[9] The ultraviolet spectrum had a band at 280 mμ characteristic of 4-pyrones.[2b]

Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.52; H, 4.45.

After extraction with ethanol, there remained 0.5 g (6%) of IIIb, mp 188–189°, undepressed on admixture with a sample of IIIb prepared by means of sodium amide (see above).

Concentration of the ethanolic extract precipitated 1.62 g of an unidentified yellow powder, mp >320°.

Condensations of β-Diketones I with Diethyl Phthalate by Sodium Hydride.—To a stirred suspension of 9.2 g (0.21 mole) of sodium hydride[11] in 50 ml of monoglyme, was added 8.1 g (0.05 mole) of benzoylacetone in 50 ml of monoglyme. After 30 min, a solution of 11.1 g (0.05 mole) of diethyl phthalate in 50 ml of monoglyme was added dropwise, and the resulting mixture was refluxed for 4 hr. The monoglyme was distilled under reduced pressure, and the residue was worked up as described above for the terephthalate reactions. Neutralization of the sodium bicarbonate solution gave a yellow solid which was recrystallized from 95% ethanol to give 7.5 g (51%) of 2-(3-phenyl-1,3-diketopropanyl)-1,3-indandione (VIIa), mp 124–126°. The infrared spectrum showed peaks at 748 cm^{-1} (*ortho* disubstitution),[9] 770 and 690 (monosubstituted phenyl)[9] and a broad band centered at 1625 cm^{-1} (β-diketone)[9].

Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.97; H, 4.10. Found: C, 73.91; H, 4.50.

A similar reaction of 0.21 mole of sodium hydride, 0.1 mole each of acetylacetone, and diethyl phthalate in 150 ml of monoglyme (refluxed 4 hr) afforded, on neutralization of the sodium bicarbonate solution, a yellow solid which was recrystallized from ethanol to give 5.25 g (46%) of 2-(1,3-diketobutyl)-1,3-indandione (VIIb), mp 127–129°. The infrared spectrum of a sample of VIIb showed peaks at 745 (*ortho* disubstitution)[1] and 1625 cm^{-1} (β-diketone).[1]

Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.97; H, 4.50.

Benzoylation of Acetylindandione X by Sodium Hydride. Independent Synthesis of VIIa.—To a refluxing suspension of 2.5 g (0.055 mole) of sodium hydride (56% dispersion in mineral oil) in 50 ml of monolgyme was added 2.0 g (0.011 mole) of 2-benzoyl-1,3-indandione[5] in 50 ml of monoglyme. After 30 min, 2.9 g (0.022 mole) of methyl benzoate in 50 ml of monoglyme was added dropwise. The mixture was refluxed with stirring for 16 hr. The monoglyme was distilled under reduced pressure and the residue was dissolved in 200 ml of water. After washing with several portions of ether, the solution was acidified to give a yellow solid which, upon recrystallization from ethanol, yielded 1.4 g (48%) of IVa, mp 122–124°. Mixture melting point with VIIa prepared from benzoylacetone and diethylphthalate was undepressed.

Condensations of β-Diketones I with Diethyl Phthalate by Sodium Amide.—To a suspension of 0.11 mole of sodium amide in 300 ml of liquid ammonia was added 8.1 g (0.05 mole) of benzoylacetone. After 30 min, 3.71 g (0.0167 mole) of diethyl phthalate in 50 ml of dry ether was added dropwise. The resulting suspension was stirred for 1 hr, and the ammonia was evaporated. The residue was worked up as described above for the terephthalate reactions. Neutralization of the sodium bicarbonate solution gave 0.91 g (9%) of the indandione VIIa, mp 120–124°.

Cyclization of Hexaketone IIIb by Sulfuric Acid to Form Bispyrone XI.—The hexaketone IIIb (1 g) was dissolved in 20 ml of concentrated sulfuric acid at 0°. The solution was allowed to stand for 30 min with occasional stirring and then poured into 300 ml of iced water. The resulting white precipitate was collected by filtration and triturated with DMF to give 0.45 g (51%) of the bis-4-pyrone XI, mp 310–315°. No ultraviolet spectrum showed absorption at λ_{max} 281 mμ (log ϵ 4.53).[2b] The infrared spectrum had a sharp peak at 1670 cm^{-1} (doubly conjugated carbonyl)[9] and no broad band such as that found in β-diketones.

Anal. Calcd for $C_{15}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.15; H, 4.82.

Attempted Cyclization of Tetraketones VIIa, b by Sulfuric Acid.—Samples (1 g) of tetraketones VIIa, b were treated with sulfuric acid as described above for hexaketone IIIb. There were recovered 0.95 g (95%) of VIIa, mp 123–125°, and 0.92 g (92%) of VIIb, mp 127–129°. The infrared spectra of these samples were identical with those of the starting tetraketones.

Reactions of Indandiones VIIa, b with Ethanolic Ammonia.—To 1 g of indandione VIIa in 50 ml of absolute ethanol was added 10 ml of liquid ammonia. The solution was evaporated to dryness and the residue was redissolved in ethanolic ammonia. The ammonia was allowed to evaporate and the solution was concentrated and cooled to precipitate 0.81 g (82%) of enamine XIIIa, mp 204–206°. The infrared spectrum showed peaks at 3450 (amino or hydroxyl group)[9] and 1590 cm^{-1} (β-diketone).[9]

Anal. Calcd for $C_{18}H_{13}O_3$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.16; H, 4.45; N, 4.81.

Similar treatment of VIIb with ethanolic ammonia gave 0.80 g (80%) of the corresponding enamine XIIIb, mp 189–190.5°. The infrared spectrum showed peaks at 3450 (amino or hydroxyl group)[9] and 1600 cm^{-1} (β-diketone).[9]

Anal. Calcd for $C_{13}H_{12}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.86; H, 4.88; N, 5.90.

Cleavage of Tetraketone VIIb to Form Indandione X.—A sample (2.3 g, 0.01 mole) of tetraketone VIIb in 100 ml of 10% sodium hydroxide solution was heated on a steam bath for 2 hr. Neutralization of the solution gave a yellow solid (mp 100–145°) which was placed in a sublimation apparatus and warmed, under reduced pressure, on a steam bath. Sublimation afforded 0.96 g (51%) of 2-acetyl-1,3-indandione (X), mp 108–110°, undepressed on admixture with authentic X. The unsublimed solid consisted of 0.89 g (39%) of unchanged VIIb, mp 127–129°, undepressed on admixture with authentic VIIb.

Attempts to Effect Condensation at Terminal Methyl Groups of Tetraketone VIIb and Hexaketone IIIb.—To a stirred suspension of 0.03 mole of sodium amide in 200 ml of liquid ammonia was added 2.3 g (0.01 mole) of solid VIIb to produce a yellow suspension. After 1 hr, 1.26 g (0.10 mole) of benzyl chloride in 50 ml of dry ether was added. No change was observed. After 1 hr, the ammonia was replaced with ether and the resulting suspension was shaken with water. The aqueous layer was added to an excess of 10% hydrochloric acid to precipitate 2.1 g (92%) of unchanged tetraketone VIIb, mp and mmp 127–129°.

Similarly, 3.30 g (0.01 mole) of hexaketone IIIb was added, with stirring, to 0.06 mole of sodium amide in liquid ammonia to produce a heavy suspension. After 1 hr, 2.52 g (0.02 mole) of benzyl chloride in 50 ml of dry ether was added. No change was observed. After 1 hr, the reaction mixture was worked up to recover 90% of the hexaketone, mp and mmp 188–190°.

The tetraketone VIIb was treated with methyl benzoate and sodium hydride in monoglyme essentially as described above for sodium hydride reactions with dimethyl terephthalate. After

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[12] It was found that the 1,3,5-triketone II (R = CH_3) could be titrated with 0.1 *N* sodium hydroxide. Hence, the acid IVb would have two neutralizable groups.

refluxing for 4 hr, the starting tetraketone VIIb was largely recovered.

Condensation of Triketone II (R = CH_3) with Diethyl Phthalate by Sodium Hydride.—To a suspension of 11.5 g (0.05 mole) of sodium hydride[11] (52% dispersion in mineral oil) in 50 ml of monoglyme was added 10.2 g (0.05 mole) of triketone II (R = CH_3) dissolved in 50 ml of monoglyme. After the mixture stirred under reflux for 20 min, 11.1 g (0.05 mole) of diethyl phthalate in 50 ml of monoglyme were added. The resulting mixture was refluxed for 6 hr and worked-up as described above for condensations of β-diketones I to give 4.81 g (29%) of XIV, mp 127–127°. The infrared spectrum showed peaks at 760 and 690 (monosubstituted phenyl),[9] 735 (*ortho* disubstitution),[9] and a broad band centered at 1620 cm^{-1} with maxima at 1700, 1650, and 1590 cm^{-1} (β-diketone).[9]

Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: C, 71.55; H, 4.31.

Registry No.—IIIa, 10437-91-9; IIIb, 10437-92-0; IVa, 10437-93-1; IVb, 10481-52-4; V, 10437-94-2; VIIa, 10437-95-3; VIIb, 10437-96-4; X, 1133-72-8; XI, 10464-99-0; XIIIa, 10437-97-5; XIIIb, 10465-00-6; XIV, 10437-98-6; sodium hydride, 7646-69-7.

Ring Enlargements. XII. N-Nitrosolactams as Ring-Enlargement Reagents[1]

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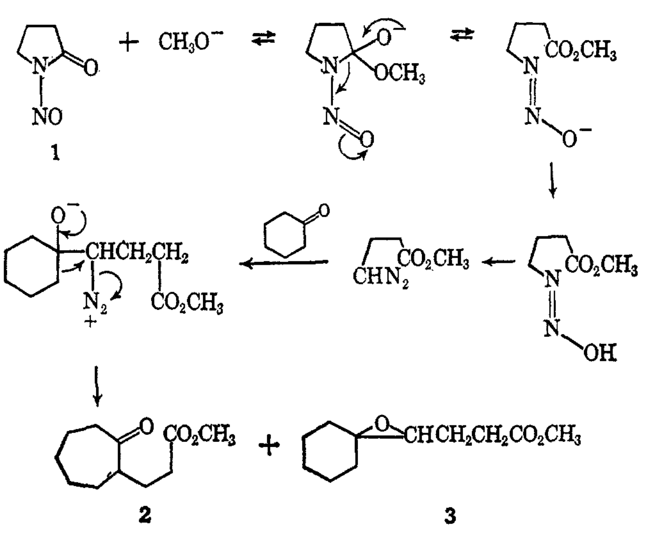
The scope and limitations of reactions involving N-nitrosolactams as ring-enlargement reagents has been investigated. It has been found that (a) cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, 4-isopropylcyclohexanone, 4-*t*-butylcyclohexanone, and 4,4-dimethylcyclohexanone all react with N-nitrosopyrrolidone-2 (in methanolic sodium carbonate) to give the corresponding methyl β-(2-ketocycloheptane)propionates in 47–64% yields; (b) cyclohexanone reacts with 3-methyl-N-nitrosopyrrolidone-2 and 4-methyl-N-nitrosopyrrolidone-2 to yield the corresponding ring-enlargement products; (c) cyclopentanone reacts with N-nitrosopyrrolidone-2 to give methyl β-(2-ketocyclohexane)propionate in only 20% yield; and (d) 5-methyl-N-nitrosopyrrolidone-2, N-nitrosopiperidone-2, and N-nitrosocaprolactam-2 fail to yield any ring-enlargement products whatsoever. As a preparative method, therefore, the reaction appears to be limited to N-nitrosopyrrolidones and cyclohexanones as the participants; within this somewhat restricted area, however, it is quite general.

One of the standard methods for effecting the diazoalkane ring enlargement of cycloalkanones involves the *in situ* generation of the diazoalkane by the action of a base on compounds of the general structure $RN{<}^{NO}_{Y}$ (where Y may be a variety of moieties including CO_2Et, $COCH_3$, $CONH_2$, etc.).[3] Although it has been shown that the mechanism of the conversion of the nitroso compound to the diazo compound is a function of the Y group,[4] the contention that the mechanism of the decomposition of nitrosourethans[5a] and nitrosoamides[5b] involves a nucleophilic attack at the carbonyl group appears to be well founded.[6] The resulting tetrahedral intermediate subsequently collapses to a diazoalkane (*via* an intermediate diazonium hydroxide) with expulsion of the Y group. Ordinarily, the Y group is of no further interest in a ring-enlargement sequence, for only the diazoalkane moiety engages the cycloalkanone. In the special instance, however, in which the Y group is doubly attached to the N-nitroso function, it must appear (as altered by solvolysis) in the ring-enlargement product. To test the preparative applications of this possibility, a series of experiments involving N-nitrosolactams as diazoalkane precursors was carried out.[7] In the simplest example a mixture of cyclohexanone, methanol, and sodium carbonate was treated at room temperature with N-nitrosopyrrolidone-2. Nitrogen was smoothly evolved, and a product was obtained in 60% yield which contained methyl β-(2-ketocycloheptane)propionate (2) contaminated with a small amount of the epoxide 3. The mechanism by which this ring-enlargement reaction presumably proceeds is illustrated in Scheme I.

Scheme I

Mechanism of Ring-Enlargement Reaction with N-Nitrosopyrrolidone-2

$$CH_3OH + Na_2CO_3 \rightleftarrows CH_3O^- + Na^+ + NaHCO_3$$



Methyl β-(2-ketocycloheptane)propionate (2) has been prepared by the action of methyl acrylate on the

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[2] Shell Oil Co. Fellow 1960–1961, Wheeler Fellow 1961–1962, and University Fellow 1962–1963.

[3] See C. D. Gutsche, *Org. Reactions*, **8**, 389 (1954).

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[7] See C. D. Gutsche and I. Y. C. Tao, *J. Org. Chem.*, **28**, 883 (1963), for a preliminary communication of the results of these experiments.