

1,3-dibromopropane (0.10 mole) as described above for the sodio salt I. The reaction afforded 9.5 g. (40%) of IIIc, m.p. 60–65° after one recrystallization from petroleum ether (b.p. 30–60°). After one recrystallization from aqueous methanol

and three from *n*-hexane, the melting point was raised to 66–67.5°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub>: C, 64.98; H, 8.39. Found: C, 64.88; H, 8.55.

## Synthesis of 3-Hydroxy-4-nitro-5-arylcyclohexanones by Claisen Condensation and Cyclization Reactions with $\beta$ -Aryl- $\gamma$ -nitro Ketones

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*Received October 15, 1964*

Examples are given of a novel, base-catalyzed ester acylation and cyclization reaction through which the  $\gamma$ -nitro ketones, obtained by Michael addition of nitromethane to benzalacetones, are converted to 3-hydroxy-4-nitro-5-arylcyclohexanones, some of which may be dehydrated to corresponding nitro enones.

The purpose of this paper is to report the finding of a novel synthesis of 4-nitrocyclohexanones, typically III, IV, and V in Chart I. Recent general interest in aliphatic nitro compounds,<sup>1–3</sup> including some precursors of hydrophenanthridines,<sup>4,5</sup> prompts now the presentation of these reactions, which were developed in 1961 in an effort to find a synthetic approach to 1-aryl-2-nitrocyclohexanes different from the well-known diene addition to  $\omega$ -nitrostyrenes.<sup>4–7</sup> It seems possible that synthetic routes *via* such nitro compounds to precursors of alkaloids in the lycorine, crinine, and caranine series ultimately may be more flexible than schemes involving Pschorr cyclization<sup>8,9</sup> or reactions of resorcinols with *o*-bromobenzoyl compounds.<sup>10,11</sup>

Although sodionitroalkanes usually react with two molecules of a very reactive, low molecular weight,  $\alpha,\beta$ -unsaturated ketone, nitrile, etc.,<sup>1,12</sup> the Michael addition of nitroalkanes to the less reactive benzylidene malonates, nitriles, and ketones generally is mono,<sup>12–20</sup> giving, in the latter case,  $\gamma$ -nitro ketones such as II. In addition to known IIa,<sup>16</sup> two other  $\gamma$ -nitro ketones, IIb and IIc, have now been prepared by addition of nitromethane to the appropriate benzylideneacetones.

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(12) See E. D. Bergman, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(13) E. P. Kohler, *J. Am. Chem. Soc.*, **38**, 889 (1916); **46**, 503 (1924).

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(15) E. P. Kohler and H. F. Engelbrecht, *ibid.*, **41**, 764, 1379 (1919).

(16) (a) E. P. Kohler and N. L. Drake, *ibid.*, **45**, 2144 (1923); (b) *ibid.*, **45**, 1281 (1923).

(17) G. D. Buckley, T. J. Elliott, F. G. Hunt, and A. Lowe, *J. Chem. Soc.*, 1505 (1947).

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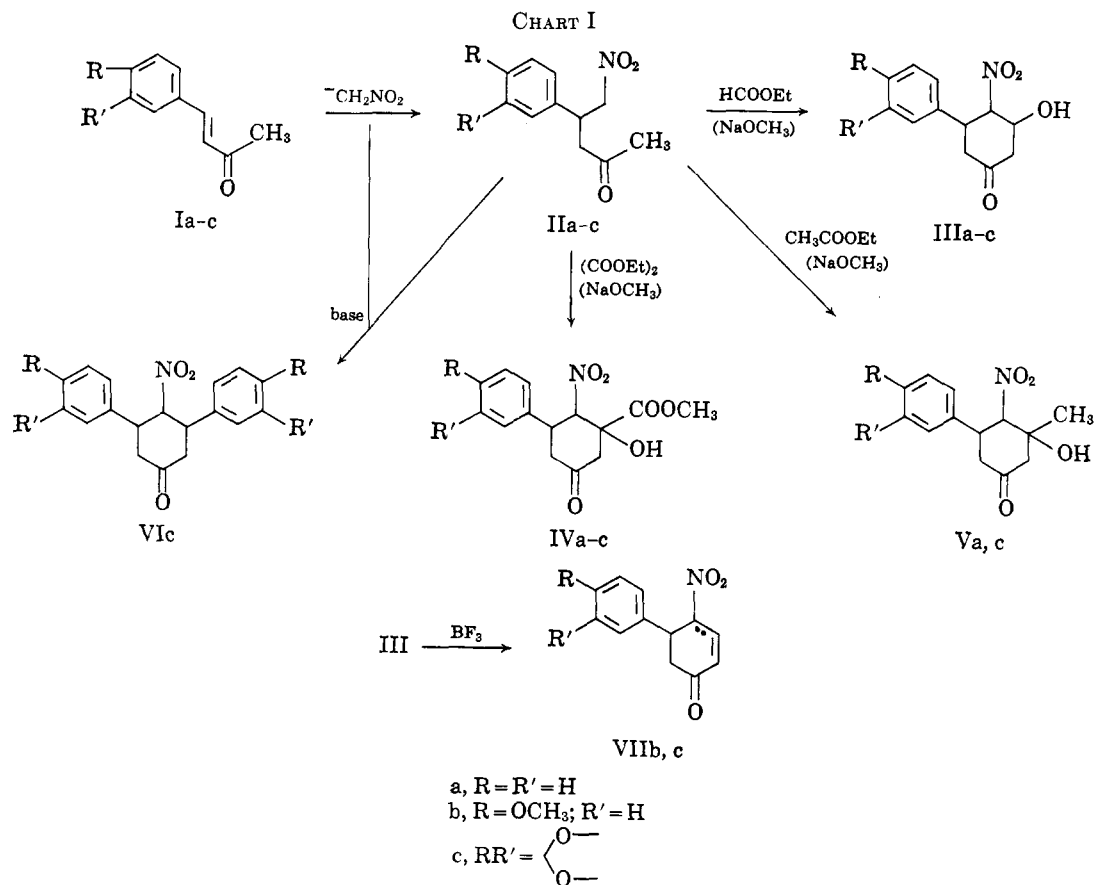
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For this reaction, sodium methoxide<sup>13–16</sup> was found to be superior to ammonia<sup>18</sup> or amines.<sup>17,19</sup> The I  $\rightarrow$  II condensation also is smoother than some alternative methods<sup>12</sup> which were given preliminary trial, for example, Michael addition of reactive methylene compounds to  $\omega$ -nitrostyrenes and addition of sodionitromethane to cinnamates or arylidenecyanoacetates; neither of these reactions was found well adapted to synthesis of  $\beta$ -aryl- $\gamma$ -nitro carbonyl compounds in which the benzene ring bears oxy substituents.

A high-melting by-product, identified as VIc, was always isolated along with IIc in the reaction of methylenedioxybenzalacetone (Ic) with sodionitromethane. The formation of VIc eventually was minimized by employing a severalfold excess of sodionitromethane. There are no less than four conceivable ways in which VIc might arise during the reaction Ic  $\rightarrow$  IIc or, as was occasionally found subsequently, during other base-catalyzed, further reactions of IIc. These are (1) direct condensation of piperonal (formed by reverse Michael or aldol reactions) with IIc; (2) formation of dipiperonalacetone and its cyclic Michael reaction with nitromethane anion; (3) reverse Michael reaction of IIc (acetone loss) to form the  $\omega$ -nitrostyrene, followed by addition of Ic and ring closure; and (4) bis Michael addition involving two molecules of Ic and one of nitromethane, followed by similar acetone loss through reverse Michael reaction, and ring closure. It is not possible at present to decide which one (or several) of these four is responsible for formation of VIc. Similar by-products (VIa,b) were not found in the sodionitromethane reactions of Ia and Ib.

In trial experiments it soon was found, as expected, that in order to promote fairly complete Claisen reactions of compounds II there had to be used at least 2, and preferably 3 or 4, equiv. of base and a similar or greater excess of acylating esters in each case. Apparently this is because of the relative ease with which the CH<sub>2</sub>NO<sub>2</sub> group initially forms its corresponding anion, so that additional base is then required to promote the (presumably less facile) formation of CO–CH<sub>2</sub><sup>–</sup>. Experiments with ethyl oxalate, of all the esters tried, were the most consistently successful, the products, obtained in fairly good yields, being cyclic hydroxynitro keto esters, IV. Ester exchange, from the ethyl of ethyl oxalate to methyl of the sodium methoxide used in excess, was observed in all three of the reactions leading to isolated compounds IV.

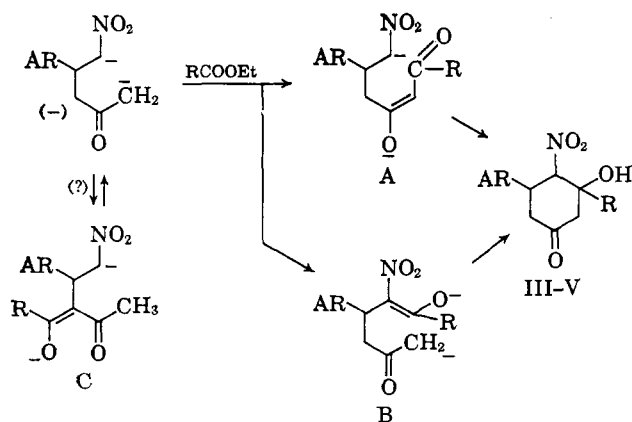


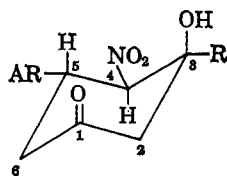
Similar condensations of II with ethyl formate, leading to compounds III, gave somewhat more erratic yields, and those with ethyl acetate, in which quite small amounts of Va and Vc were isolated in two cases, were still poorer. These facts accord generally with much past experience in reactions of these three commonly used acylating esters; however, they shed little or no light upon the question of any exact manner in which III, IV, and V are formed, which will now be discussed briefly.

Since the anion formed from an  $\alpha$ -nitromethylene group probably is somewhat more resonance-stabilized ( $\rightleftharpoons$  *aci* form) than that derived from the methylene adjacent to a ketone, the first step in these reactions, many of which were observed to be initially rather slow, may be acylation of the terminal, and least hindered, COCH<sub>3</sub> group. This would be followed by aldol closure involving the new terminal group of the resulting 1,3-dicarbonyl compound with the *aci*-nitro anion, *e.g.*, route A below. However, in the absence

of further specific information about intermediates, none of which have been isolated yet in pure state from any of the condensations, one cannot exclude the *a priori* less attractive, although reasonable, route B involving initial attack of ester upon the nitro- $\alpha$ -methylene, followed by interaction of the new nitro ketone anion with the methyl ketone. In either event it is clear that III, IV, and V are the result of final formation of a six-membered ring from intermediate(s) capable of ring closing in the end to a relatively stable ketol form. There may be a certain amount of acylation at the ketone methylene group, giving C, but subsequent aldol cyclization of this vinylogous carboxylate would have to involve the competitively unlikely closure of a four-membered ring, as would also cyclization in any other direction of intermediates A and B. Thus, although there is a certain ambiguity for now concerning them, the two most likely routes lead to the same final product, and in fact it is possible that both actually are followed.

A molecular weight determination in the case of the structurally simplest member, IIIa, of this group of analogous cyclic ketols gave a result precisely agreeing with structure IIIa and excluding various conceivable alternative, dimeric structures for the compound. The n.m.r. spectrum of IIIa, for which the data and their interpretation are to be found in the Experimental part, not only conclusively proved the structure of the phenyl-*sec*-nitro-*sec*-hydroxy ketone IIIa, but also established clearly that its stereochemical configuration is that shown (R = H; AR = phenyl). This outcome was anticipated in part, since it seemed likely that the unstrained 4,5 diequatorially *trans*<sup>7</sup> structure would be most preferred, and certainly have ample opportunity to develop, during reactions in-





volving a variety of electron-delocalized, anionic intermediates. It is likely that the remaining cyclic ketols, IIIb and c, IV, and V, are of the same general configuration (R = H, COOCH<sub>3</sub>, and CH<sub>3</sub>, respectively), although at present, proof of this statement cannot be drawn from their more complex n.m.r. spectra. The structures, if not the exact stereochemistry, of the remaining crystalline compounds, III, IV, and V, rest at present upon the consistent body of evidence gained in their synthesis, correct analytical figures in each case, and the substantial support provided by a quite consistent set of infrared spectra. The latter, in every case clearly showed relatively strong hydroxyl (2.9–3.0  $\mu$ ), ketone (5.8–5.85  $\mu$ ), and nitro (6.4–6.46  $\mu$ ) peaks; and compounds IV additionally had infrared ester (*ca.* 5.75  $\mu$ ) absorption.

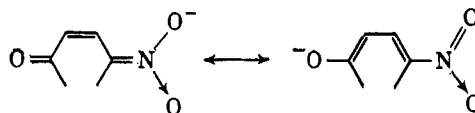
Concerning the formation of these ketols, one may accept its analogy with already known, similar, spontaneous cyclic ketol formation in nonnitrogenous, polycarbonyl compounds.<sup>12,21</sup> There is the difference between the present cyclizations and some of those already known (which do not involve strongly enolic intermediates) that the present ring closures appear to occur spontaneously only after the enolic, noncyclic, acylated nitro ketones have been generated from their anions through protonation. Thus, in several instances, notably with compounds IIIa and b, IVb, and Va, it was observed clearly that the major part of the material, after the acylation reactions in the presence of excess base, dissolved initially when water was added, and so must have been at that stage the acyclic enol. All the cyclic ketols, III–V, after being isolated through acidification of sodium enolates, were no longer alkali-soluble.

Further evidence for the presence of the unaltered nitro group in the ketols, and the fact that it was situated in a hindered location, was adduced by hydrogenations, which were tried with several of the nitrohydroxycyclohexanones in the presence of nickel and palladium catalysts. In each case initial uptake of hydrogen (1–2 equiv.) took place with only moderate speed, and uptake of the remaining gas (to a total of 3 molar equiv.) took place quite slowly. None of the resulting crude products, however, have been identified so far *per se*, as salts, or after acetylation or other reactions. For the most part they are unstable mixtures consisting partly of neutral material, signifying the likelihood that typically "abnormal" changes<sup>16b</sup> of intermediate  $\beta$ -phenethylimine moieties had occurred, perhaps complicated further here as well by reverse aldol or other degradations of hydroxy ketone.

A question perhaps involved in the various condensations with compounds II, concerning which so far there also is at hand no clear-cut evidence, is to what extent

Nef hydrolysis<sup>7,22</sup> of the nitro group, known to take place readily with  $\beta$ -arylnitroalkanes, may intervene during the acylation–cyclization processes. It seems likely that its occurrence to some extent is inevitable and at least partly responsible for some lowering of the yields of III and V obtained *via* respective, relatively slow acylations. The use of condensing agents other than sodium methoxide presumably might increase the efficiency of these reactions, which at present could hardly be described as maximal. However, the few attempts to employ sodium hydride, and worse yet sodamide, instead of sodium methoxide were unsuccessful. Conversely, several deliberate attempts to provoke Nef reaction of III, V, and VII by exposure to base, hydrolysis, and addition of acid, in the hope of obtaining 3-arylphenols and thus additional evidence of structure, were unrewarding, ill-defined mixtures of phenolic (or enolic) and nitro compounds being the result. Again, probably partial reverse aldol reactions were responsible for these effects.

Although it has not yet been possible to dehydrate compound IIIa without undue decomposition to a well-characterized, corresponding nitro enone, the reaction appears to have been successful in the cases of IIIb and IIIc. Of several acidic reagents tried for the conversion of these, respectively, to correctly analyzing VIIb and VIIc, the best so far found has been boron trifluoride. The infrared disappearance of hydroxy peak, shift of ketone peak to 5.93  $\mu$ , and retention of the nitro (6.45- $\mu$ ) band accompanying these dehydrations constitute good additional evidence for the structures of compounds III and VII. The somewhat unusual bands observed at longer wave lengths in the ultraviolet spectra of compounds VII (see Experimental part) indicate that an extended resonance effect probably is operative in the vinylogous  $\alpha$ -nitro ketone grouping, an explanation which is in accord with the observed alkali-solubility of the nitro enones.



For any proposed further elaboration of lycorine-related compounds from the c series of substances presented here, it would be necessary to insert a two-carbon moiety at position 3. At least in principle, this might be achieved in the following ways: (1) by using some suitable three-carbon moiety, or a precursor thereof, originally in acylating IIc; (2) by further Michael reactions of enones VII; or (3) by acylation of a 3-substituted VII, presuming that there might be a sufficient vinylogously activating influence of 4-nitro and/or 1-keto group(s) upon a carbon atom attached at position 3. In respect to 1 it can be said only that attempts so far to acylate and ring close compounds II with ethyl propiolate and sundry other agents (see Experimental) have not given recognizable products. With the idea 2 in mind, some preliminary efforts were made to carry out Michael addition of malonates, acetoacetates, etc., to compounds VII but so far these have been unsuccessful, again

(21) See, e.g., A. L. Wilds, *et al.*, *J. Am. Chem. Soc.*, **72**, 5794 (1950); W. S. Johnson, *et al.*, *ibid.*, **78**, 6285 (1956); G. N. Walker, *ibid.*, **77**, 3664 (1955); **79**, 3508 (1957); N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2348 (1964).

(22) E. E. Van Tamelen and R. J. Thiede, *J. Am. Chem. Soc.*, **74**, 2615 (1952).

presumably because of facile reverse aldol reaction and decomposition in the presence of strong bases. The low yields of compounds V practically preclude their further use in any scheme based upon aforementioned possibility 3. Attempted boron trifluoride dehydration of compounds IV, as well as attempted acylation and ring closure of II with acetic anhydride-boron trifluoride, were abortive, as described in the Experimental part. Therefore, at present one is inclined to believe that the feasible *direct* route, if any, from these nitrocyclohexanones toward 7-arylhydroindoles may depend upon first finding successful means for appropriate Michael additions to VII, a proposal now awaiting the test of further work.

### Experimental<sup>23</sup>

**Benzalacetones (I).**—Ia and Ib were purchased, and piperonalacetone (Ic) was prepared by Claisen-Schmidt condensation as follows. A solution of 200 g. of piperonal in 208 ml. of acetone and 200 ml. of methanol was treated dropwise with 10% sodium hydroxide solution, a small amount of which provoked exothermic reaction, the appearance of a yellow color, and finally, after addition of 5–10 ml. of the base, separation of crystals. These were collected, after chilling the suspension, and washed with ethanol. From the filtrate, on further standing, a second crop was isolated; the total yield of yellow crystals averaged 246 g. (97%), m.p. *ca.* 135–155° with prior sintering or partial melting *ca.* 100–105°. This material apparently was a somewhat impure mixture of *cis* and *trans* isomers, and may also have contained some di-(3,4-methylenedioxyethyl) ketone, but was usually suitable for use in further work without purification.

**4-Aryl-5-nitro-2-pentanones (II).** IIa.—A solution of 5 g. (0.218 g.-atom) of sodium in 80 ml. of methanol was treated first with 13 ml. (15 g., 0.246 mole) of nitromethane and then with a warm solution of 25 g. (0.171 mole) of benzalacetone in 20 ml. of methanol. The crystals dissolved after about 5-min. swirling. When the solution was allowed to stand 0.5 hr., a mild, slowly exothermic reaction occurred resulting in a red color. The solution was chilled and treated with 15 ml. of acetic acid, whereupon immediate crystallization occurred. After the addition of a little water the product was collected and dried: 17.5 g. (49%); m.p. 89–93°, raised by trituration with ether to 97–98° (lit.<sup>16</sup> m.p. 99–100°);  $\lambda_{\text{max}}^{\text{Nujol}}$  5.85 and 6.46  $\mu$ . Material of this grade of purity sufficed for further work, as did also that from larger runs which usually was contaminated with some higher melting impurities. The nitro ketone was not very stable, but had a tendency, especially in the presence of solvents and bases, to form higher melting substances, *inter alia* probably VIa.

IIb.—To a solution of sodionitromethane, similarly prepared from 13 g. (0.565 g.-atom) of sodium, 100 ml. of methanol, and 32.5 ml. of nitromethane, was added 50 g. (0.313 mole) of 4-(*p*-methoxyphenyl)-3-buten-2-one. Upon warming the suspension gently for 3 min., the material dissolved; an exothermic effect, lasting for about 10 min., was then observed when the solution was allowed to stand, and a deep red color appeared. After treatment of the solution with 36 ml. of acetic acid and dilution with water, the product was extracted with ether. The ether solution was twice washed with water, dried over magnesium sulfate, and evaporated to small volume. The residue crystallized in ether, giving several crops of material totaling 34 g. (50%), m.p. 83–85°. A sample, recrystallized from methanol, had m.p. 86–87°;  $\lambda_{\text{max}}^{\text{Nujol}}$  5.82, 6.18, and 6.45  $\mu$ .

*Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>NO<sub>4</sub>: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.46; H, 6.48; N, 6.12

A by-product of type VI was not found in this case.

**Ic and By-product VIc.**—To sodionitromethane, prepared from 14 g. (0.609 g.-atom) of sodium in 100 ml. of methanol and 35 ml. of nitromethane, was added 50 g. (0.264 mole) of crude piperonalacetone. The suspension was boiled on a steam cone for 10 min. and allowed to stand and cool during another 10 min.

Acetic acid (40 ml.) was added, and, after immediate dilution with several volumes of cold water, the product was extracted with ether. The ether solution was washed twice with water, dried over magnesium sulfate, filtered, and, after being seeded with a previously prepared sample (see below) of VIc, was allowed to stand and evaporate gradually (*ca.* 3 hr.) until no further separation of VIc occurred. This material was removed by filtration and washed with ether; yield of the by-product was usually *ca.* 10–15 g. Recrystallized from methanol, it consisted of nearly colorless crystals, m.p. 215–216.5°. The infrared spectrum (Nujol) had peaks at 5.85 and 6.43  $\mu$ .

*Anal.* Calcd. for C<sub>20</sub>H<sub>17</sub>NO<sub>7</sub>: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.66; H, 4.62; N, 3.61.

The ether filtrate, after removal of VIc, was evaporated to a volume of *ca.* 50 ml. without excessively heating the red, oily residue, which was then taken up in *ca.* 30 ml. of methanol and 50 ml. of benzene; after seeding with a sample of IIc and allowing crystallization to occur, the product was collected and washed with a little methanol. There was obtained, on the average in a number of runs, 10–12.5 g. (15–19%) of crystals, m.p. 92–95°. A pure sample was prepared by further recrystallization from methanol giving colorless crystals: m.p. 96.5–98.5°,  $\lambda_{\text{max}}^{\text{Nujol}}$  5.85 and 6.45  $\mu$ .

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>5</sub>: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.36; H, 5.20; N, 5.56.

Prior to developing this procedure, early smaller scale attempts to react piperonalacetone with more nearly equivalent amounts of sodionitromethane gave viscous, red-brown, gummy material, from which the 3,5-bisaryl product VIc alone could be isolated by trituration with methanol. Only by using excess sodionitromethane and as short a reaction time as possible, with warming to assist the dissolution of starting enone, as described, were acceptable quantities of Ic obtained; this product was first obtained in crystalline form after standing in the presence of methanol.

**3-Hydroxy-4-nitro-5-arylcyclohexanones (III).**—Condensation of 4-aryl-5-nitro-2-pentanones with ethyl formate may be exemplified by preparation of IIIb. Freshly prepared, dry sodium methoxide, from 8 g. (0.348 g.-atom) of sodium, and 20 g. (0.084 mole) of compound IIb in dry ether were treated with an excess (*ca.* 40 ml.) of ethyl formate, and, after the initial reaction had taken place, the yellow suspension was allowed to stand 2–3 hr. (slow effervescence). The suspension was chilled and diluted with cold water; most of the material appeared to dissolve in the aqueous layer as long as the mixture was still alkaline. The aqueous layer, after acidification at ice temperature with 15% hydrochloric acid, deposited yellow crystals; these were collected and, after washing with water and air drying, were triturated with ether. A further small amount of product was obtained from the original ether solution, after acidification with a little hydrochloric acid, washing with water, drying over magnesium sulfate, and evaporation to small volume. The total yield of product, m.p. 167–171° dec., was 10.7 g. (48%). A pure sample, obtained by recrystallization from ethyl acetate as colorless crystals, had m.p. 190–191° dec.;  $\lambda_{\text{max}}^{\text{Nujol}}$  2.93–3.01 (doublet), 5.82, and 6.42  $\mu$ . The compound was no longer soluble in dilute alkali.

*Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>NO<sub>5</sub>: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.97; H, 5.88; N, 5.58.

IIIa.—Similar condensation of IIa (30.0 g., 0.145 mole) with ethyl formate (*ca.* 40 ml.) and sodium methoxide (from 10.4 g., 0.452 g.-atom, of sodium) in dry ether, followed by a 16-hr. period of stirring at room temperature and subsequent treatment with water, gave, after acidification of the aqueous layer with acetic acid, filtration, washing with water, air drying, and trituration with ether, 19.2 g. of crystals, m.p. 164–167°. Recrystallization from ether afforded nearly pure material, m.p. 193–195° dec. A further 1.8 g. of product was obtained on working up the original ether solution, bringing the yield to 21 g. (62%). A pure sample, obtained by recrystallization from ethyl acetate, had m.p. 194–196° dec.;  $\lambda_{\text{max}}^{\text{Nujol}}$  3.00, 5.86, and 6.46  $\mu$ .

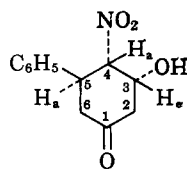
*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>4</sub>: C, 61.27; H, 5.57; N, 5.96; mol. wt., 235. Found: C, 61.36; H, 5.71, 5.68; N, 5.76, 5.79; mol. wt. (osmometric, chloroform vapor pressure), 234.

When this condensation using 17.5 g. of IIa was allowed to stand only 5 hr., there was isolated only about 1.0 g. of IIIa, m.p. 193–194° dec., and 14.2 g. of IIa was recovered.

The n.m.r. spectrum of IIIa, obtained with a Varian A-60 spectrometer at 60 Mc./sec., using tetramethylsilane as internal

(23) Melting points were taken in a stirred, silicone-oil Hershberg bath with a standard 360° thermometer, and are uncorrected. In long experience many literature melting points have been reproduced directly in this apparatus.

reference and dimethyl sulfoxide as solvent, was fully interpretable, displaying aromatic protons (446 c.p.s.; narrow multiplet, intensity *ca.* 5) and four methylene protons adjacent to carbonyl (multiplet centered at 165 c.p.s.). In addition the following significant values were ascertained through first-order analysis. The hydroxy group proton, a doublet at 365 c.p.s. ( $J = ca.$  4.7 c.p.s. with H-3) disappeared upon addition of deuterium oxide, and at the same time the H-3 multiplet at 290 c.p.s. collapsed appreciably, to a half-height width of *ca.* 6 c.p.s., which established the 3-hydroxy group as secondary. The H-3 signal at 290 c.p.s. in the oxydeuterated molecule was seen as a 1:3:3:1 quartet, explicable only on the basis that this hydrogen (H-3e) is equatorial and has small and nearly equal spin coupling to three neighboring protons.<sup>24</sup> The proton on the nitro-bearing C-4, flanked only by those on C-3 and C-5, appeared at 348 c.p.s. as a doubled doublet, clearly showing both a-e ( $J = ca.$  2.5 c.p.s.) and a-a coupling ( $J = ca.$  11.6 c.p.s.); thus, since H-3e is equatorial, both H-4 and H-5 must be axial. The H-5a signal appeared as a multiplet at 243 c.p.s., as expected for an axial proton attached to a carbon also bearing phenyl. The complete analysis of the spectrum thus leads unequivocally to the following assignments.



**IIIc.**—Condensation of 15 g. of IIc with 20 g. of ethyl formate in the presence of sodium methoxide (from 3.1 g. of sodium) in ether for 3 hr. similarly gave a crude, red product from which *ca.* 1.0 g. of crystals, m.p. 203–205° dec., were isolated by trituration with ether–ethyl acetate. Recrystallization from ethyl acetate raised the melting point to 210–211° (dec. following);  $\lambda_{\text{max}}^{\text{Nujol}}$  2.95, 5.84, and 6.41  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{15}\text{NO}_6$ : C, 55.91; H, 4.70; N, 5.02. Found: C, 55.89; H, 4.66; N, 4.82.

**3-Carbomethoxy-3-hydroxy-4-nitro-5-arylcyclohexanones (IV).**—Condensation of 4-aryl-5-nitro-2-pentanones with ethyl oxalate was carried out as follows for IVa. To freshly prepared dry sodium methoxide from 7 g. (0.34 g.-atom) of sodium, suspended in 200 ml. of dry ether, was added 20 g. (0.0965 mole) of IIa in 200 ml. of benzene, and 44 g. (0.30 mole) of ethyl oxalate. The suspension was magnetically stirred 12 hr. at *ca.* 35°. After chilling, the mixture was treated with water and 20 ml. of acetic acid. The crystals which separated were collected, washed with water and ether, and air dried; the yield of nearly pure product (m.p. 168–172°) was 14.4 g. (51%). A pure sample, recrystallized from ethyl acetate, had m.p. 177–179° dec.;  $\lambda_{\text{max}}^{\text{Nujol}}$  3.02, 5.70, 5.81, and 6.43  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{15}\text{NO}_6$ : C, 57.33; H, 5.16; N, 4.78. Found: C, 57.23; H, 5.20; N, 4.59.

**IVb.**—Similar condensation of 12 g. (0.0543 mole) of IIb with 11.8 g. (0.081 mole) of ethyl oxalate in the presence of sodium methoxide prepared from 4.0 g. (0.174 g.-atom) of sodium with the omission of benzene in the foregoing procedure, for 5.5 hr., gave material which was soluble initially in the aqueous alkaline phase. After acidification with 18% hydrochloric acid, the crude, brown oil was extracted with ether–ethyl acetate. The organic solution was washed with two portions of water, dried over magnesium sulfate, and evaporated. The residual red oil crystallized in the presence of ether, giving 4.5 g. (26%) of product, m.p. 154–160° dec. Recrystallization from ethyl acetate raised the melting point to 169–171° dec.;  $\lambda_{\text{max}}^{\text{Nujol}}$  2.89, 5.78–5.81 (unresolved doublet), and 6.41  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{17}\text{NO}_7$ : C, 55.72; H, 5.30; N, 4.33. Found: C, 56.23; H, 5.42; N, 4.12.

**IVc.**—Condensation of 30 g. (0.12 mole) of IIc with 52 g. (0.356 mole) of ethyl oxalate and sodium methoxide from 8.3 g. (0.36 g.-atom) of sodium, in ether–benzene as in the above procedure and work-up (acetic acid was used to acidify the reaction mixture), gave, after washing with ether and water, a maximum yield (nine runs) of 27.5 g. (68%) of product, m.p. 187–194° dec. The pure sample, recrystallized from ethyl acetate, had m.p. 203–205°;  $\lambda_{\text{max}}^{\text{Nujol}}$  2.92, 5.75–5.80 (doublet), and 6.44  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{15}\text{NO}_6$ : C, 53.41; H, 4.48; N, 4.15. Found: C, 53.47; H, 4.67; N, 3.99.

**3-Hydroxy-3-methyl-4-nitro-5-arylcyclohexanones (V).** **Va.**—To dry sodium methoxide, freshly prepared from 6.6 g. (0.287 g.-atom) of sodium, was added a solution of 20.9 g. (0.101 mole) of 4-phenyl-5-nitro-2-pentanone in 100 ml. of ethyl acetate. A rather prolonged (*ca.* 1 hr.), mildly exothermic reaction was observed as the base dissolved and a red-brown solution formed. After standing another hour, the solution was treated at ice temperature with water, and ether was added. After shaking and separating, the dark, aqueous phase was acidified weakly in the cold with dilute hydrochloric acid. A very deep red oil separated and crystallized partly on scratching. The crude product was washed (by decantation or as an ether solution) with water. A magnesium sulfate dried, ether solution of the material, after evaporation to small volume and the addition of a little methanol, deposited 1.8 g. (0.7% yield) of crystals which, after being washed with ether containing a small amount of methanol, had m.p. 191–194°. Recrystallization from ethyl acetate raised the melting point to 196–198°;  $\lambda_{\text{max}}^{\text{Nujol}}$  2.98, 5.83, and 6.38  $\mu$ ; the sample was dried *in vacuo* at room temperature.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{15}\text{NO}_4$ : C, 62.64; H, 6.07; N, 5.62. Found: C, 62.39; H, 6.32; N, 5.54.

**Vc.**—Similar condensation of 3.1 g. of IIc with ethyl acetate (40 ml.) using sodium methoxide (from 3.0 g. of sodium) gave *ca.* 0.3 g. of methanol-triturated crystals: m.p. 203–206° dec., raised by recrystallization from ethyl acetate to 227–229° (after drying *in vacuo*);  $\lambda_{\text{max}}^{\text{Nujol}}$  2.95, 5.83, and 6.38  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{15}\text{NO}_6$ : C, 57.33; H, 5.16; N, 4.78. Found: C, 57.64; H, 5.34; N, 4.67.

Prolonged drying of either of these compounds *in vacuo* at *ca.* 80° tended to lower the melting point and result in less accurate analytical figures.

**Dehydration of 3-Hydroxy-4-nitro-5-arylcyclohexanones to the Corresponding Enones.** **VIIb.**—A suspension of 2 g. of compound IIIb in *ca.* 20 ml. of boron trifluoride–acetic acid complex was stirred at room temperature for 0.5 hr., until the solid material had dissolved. The dark green solution was treated with ice and water. The green gum which formed initially gradually crystallized; the crude product was collected, washed with water, air dried (1.7 g.), and recrystallized from ether and cyclohexane. There were obtained pale yellow crystals: m.p. 93–94°; the compound did not give an appreciable ferric chloride test;  $\lambda_{\text{max}}^{\text{Nujol}}$  5.93, 6.20 (mod.), and 6.45  $\mu$ , and no hydroxyl band;  $\lambda_{\text{max}}^{\text{EtOH}}$  220, 271–274, 334–339, and 409  $m\mu$  ( $\epsilon$  17,160, 3560, 5030, and 3710, respectively).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{13}\text{NO}_4$ : C, 63.15; H, 5.30; N, 5.67. Found: C, 63.46; H, 5.42; N, 5.71.

**VIIc.**—The similar reaction of 10 g. of compound IIIc with *ca.* 70 ml. of boron trifluoride–acetic acid for 5 min. resulted in a brown solution and, after hydrolysis, yellow-brown, crystals which were collected and washed with water; the yield of crude nitro enone (m.p. 136–141° dec.) was 8.8 g. (94%). Recrystallization from methanol gave a pure sample, pale yellow-orange crystals: m.p. 146–147.5° dec.;  $\lambda_{\text{max}}^{\text{Nujol}}$  5.92 and 6.45  $\mu$  (and no hydroxyl peak);  $\lambda_{\text{max}}^{\text{EtOH}}$  285–288, 334–340, and 406–414  $m\mu$  ( $\epsilon$  5200, 4760, and 4640, respectively) and broad inflection *ca.* 220  $m\mu$  ( $\epsilon$  9250).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{11}\text{NO}_5$ : C, 59.77; H, 4.24; N, 5.36. Found: C, 59.76; H, 4.30; N, 5.42.

These two cyclic nitro enones were soluble in bases. After treatment with alcoholic alkoxides and subsequent (aqueous) acidification, ill-defined, red, oily mixtures of enolic or phenolic and nitro compounds were isolated. Similar products resulted from attempted reactions with ethyl malonate and ethyl acetoacetate in the presence of sodium methoxide.

**Attempted reaction of ester IIIc with boron trifluoride** gave only a small amount of a yellowish, crystalline compound, m.p. 176–181° dec., apparently the same as that obtained in somewhat better yield from reaction of IIc with acetic anhydride–boron trifluoride, as described under the next heading.

**Additional Experiments with IIc.**—The  $\gamma$ -nitro ketone was recovered unchanged in varying amounts, or else intractable, red-brown oils and resins were formed, after attempted condensation with the following reagents: (1) ethyl sodioformyl acetate, (2) ethoxyacrylonitrile and bases, (3) ethyl chloroformate and sodium methoxide or sodium hydride, (4) ethyl malonate and sodium methoxide, (5) ethyl cyanoacetate and sodium methoxide, (6) formyl acetic anhydride, (7) malonaldehyde diethyl-

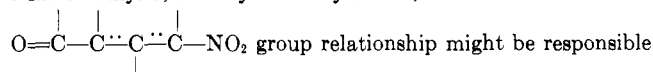
acetal, (8) glyoxal, (9) dimethylacetylene dicarboxylate and sodium alkoxide, (10) acetic anhydride, (11) oxalyl chloride with boron trifluoride or phosphorus oxychloride, and (12) chloroform and sodium alkoxide.

Attempted reaction of IIc (12.3 g.) with ethyl acetoacetate (8.2 g.) or ethyl propiolate (7.3 g.) in the presence of sodium methoxide (from 4.6 g. of sodium) gave in each case only compound VI (1–2 g.), m.p. 214–215° dec., identical (mixture melting point, spectra) with a sample of VI prepared as described above, in addition to much red-brown, intractable gum.

The reaction of IIc (5.4 g.) with acetic anhydride (7.5 g.) and boron trifluoride etherate (23 ml.) did not lead to VIIc, but rather there was isolated, after hydrolysis with sodium acetate solution, extraction, trituration with ether–ethyl acetate, and recrystallization from methanol, a pale yellow, crystalline compound: m.p. 179–181° dec.;  $\lambda_{\text{max}}^{\text{Nujol}}$  6.11 and 6.40–6.51  $\mu$ ;  $\lambda_{\text{max}}^{\text{EtOH}}$  255 and 352  $\mu$  ( $\epsilon$  13,810 and 11,710, respectively) with an inflection ca. 300  $\mu$  ( $\epsilon$  5060).

Anal. Calcd. for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.91; H, 4.88; N, 4.96.

The formula and spectra of this substance lead to a first (tentative) assignment of its structure as either 1-methyl-2-nitro-3-acetyl-5,6-methylenedioxyindene or 1-methyl-2-acetyl-3-nitromethyl-5,6-methylenedioxyindene, in either of which the



group relationship might be responsible for the abnormally long wave length of carbonyl infrared absorption.

**Acknowledgment.**—The laboratory work was done with the technical assistance of Mrs. Ruth Ann MacAllister. We also thank Mr. Louis F. Dorfman, Mr. George Robertson, Mr. Rudolf Oeckinghaus, Miss Natalie Cahoon, Miss Jan Siragusa, and other members of the Technical Services Laboratories for microanalytical and spectral data, and Mrs. Angelina Aretakis for aid in checking the literature.

## A Convenient Synthesis of 3 $\beta$ -Hydroxyandrost-4-en-17-one<sup>1a</sup>

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Received December 3, 1964

3 $\beta$ -Hydroxyandrost-4-en-17-one (1) was synthesized by reduction of 17-hydroxypregn-4-ene-3,20-dione (2) with lithium tri-*t*-butoxyaluminumhydride, followed by side-chain cleavage with lead tetraacetate. This method yields almost exclusively the 3 $\beta$ -hydroxy epimer (1) uncontaminated with saturated 3-hydroxy-5 $\alpha$ -androst-17-one.

3 $\beta$ -Hydroxyandrost-4-en-17-one (1), although it is known, is not readily obtained in pure form. Because of its formation from androst-4-ene-3,17-dione in the presence of reduced diphosphopyridine nucleotide and an acetone powder of sheep adrenal microsomes,<sup>2a</sup> it became necessary to prepare a pure sample for comparison and for further biochemical studies. The allylic alcohol 1 and similar compounds have recently become prominent in the consideration of metabolic pathways and the mechanism of enzymic reduction of  $\Delta^4$ -3-keto steroids.<sup>2b</sup>

The method of Ruzicka, *et al.*,<sup>3</sup> involving addition of hydrogen chloride to 3 $\beta$ -hydroxyandrost-5-en-17-one followed by dehydrochlorination, appeared to be inconvenient and might be expected to yield a mixture of  $\Delta^4$  and  $\Delta^5$  isomers.

Reduction of androst-4-ene-3,17-dione with sodium borohydride in 2-propanol, under the conditions described by Kupfer<sup>4</sup> as suitable for the conversion of pregn-4-ene-3,20-dione to 3 $\beta$ -hydroxypregn-4-en-20-one, apparently caused reduction of the 17-ketone at approximately the same rate as the 3-ketone, as evi-

denced by the parallel diminution of the infrared absorption intensities at 1740 and 1675 cm.<sup>-1</sup>. A more indirect but successful route (Scheme I) involved reduction with lithium tri-*t*-butoxyaluminumhydride<sup>5,6</sup> of 17-hydroxypregn-4-ene-3,20-dione (2) to a mixture of pregn-4-ene-3 $\beta$ ,17,20-triols (3) epimeric at C-20. The 17,20-glycol was cleaved by lead tetraacetate in glacial acetic acid to yield the 17-ketone.<sup>7</sup> The product 1 was converted to 3 $\beta$ -benzoyloxyandrost-4-en-17-one (4), which crystallized readily from methanol or acetone. Hydrolysis then yielded the free 3 $\beta$ -hydroxyandrost-4-en-17-one (1) which, after several crystallizations from hexane, melted at 133.5–134°.

During the course of this work, Thomas and Dorfman<sup>8</sup> described a similar synthesis of 3 $\beta$ -hydroxyandrost-4-en-17-one (1) using sodium borohydride in methanol for the reduction. They obtained a product of somewhat lower melting point (124°). In our experience, borohydride reduction of 17-hydroxypregn-4-ene-3,20-dione (2) in 95% ethanol or 2-propanol, followed by lead tetraacetate cleavage, gives a mixture of 3 $\beta$ -hydroxyandrost-4-en-17-one (1, 70%) and the saturated 3 $\beta$ -hydroxy-5 $\alpha$ -androst-17-one (20%) together with minor quantities of other products. 3 $\beta$ -Hydroxy-5 $\alpha$ -androst-17-one has a mobility very close to that of the allylic alcohol 1 in several thin layer chromatographic systems; its presence is readily detected by gas-liquid chromatography. Sondheimer,

(1) (a) Publication No. 1199 of the Cancer Commission of Harvard University, supported by Public Health Service Grant No. CA02421-10 and CA01393-13 from the National Cancer Institute and a grant from the American Cancer Society, Inc.; (b) Predoctoral Fellow of U. S. Public Health Service; (c) Permanent Faculty Fellow of the American Cancer Society.

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