clear that the steric effects of the alkyl groups have a direct influence on the approach of the peracid to the carbonyl. This will affect mainly K and not k, and the over-all result is a lower rate. The rate constant of 3-methylcyclopentanone is lower than that for cyclopentanone, and the bicyclic ketones, camphor and fenchone, in which the keto group is surrounded by the methyl groups and the carbon skeleton, have much lower values.

Indanone has a lower rate constant than cyclopentanone as is expected due to the restriction in the polarization of the carbonyl which implies a lowering in resonance energy of this compound, going to the addition product (C). A methoxy group at C-5 increases the rate of oxidation in indanone and probably this is due to a higher migration capability of the aromatic group that increases k in comparison with the unsubstituted ketone.

In the cyclohexanones, 2-methyl-, 2,2-dimethyl-, and 3-methylcyclohexanones are less reactive than cyclohexanone owing to steric considerations; their rate constants can be easily explained on these grounds, since the oxidation slows as the groups get nearer and more bulky. In the 4-methyl- and 4-*t*-butylcyclohexanones it is at first sight surprising to find an increase in the rate, which is higher in the *t*-butylcyclohexanone.

We can consider the peracid oxidation as an addition reaction in which the anion attacks the tertiary carbonium ion of the polarized carbonyl group. Any factor stabilizing this ion in the transition state will favor the rate of oxidation.

There are several previous cases of 1:4 interactions in the cyclohexane. Owen[13] suggested the formation of a 1,4-oxygen bridge in the reaction of halohydrins with base. Bennett[14] suggested the presence of a cyclic halogenonium ion in the dehalogenation reactions of 1,4-dihalocyclohexanes and Goering[15] proposed a 1,4-bromonium ion bridge in the rearrangement of dibromocyclohexanes with ferric bromide. More conclusive was the solvolysis of *trans*-4-methoxycyclohexyl tosylate studied by Noyce.[16,17] This author and his co-workers suggested that anchimeric assistance is possible through an intermediate cyclic nonclassical ion in which the cyclohexane adopts the boat form, when the electrons on oxygen can stabilize the positive charge on the carbon. In the 4-methyl- and 4-*t*-butylcyclohexanones some type of 1,4-interaction must be operating which promotes reaction.[18]

Tetralone oxidation is 144 times slower than cyclohexanone and this result can be explained as being due to the decrease in resonance energy. A 6-methoxy group increases the migration capability of the aromatic ring and therefore k and the observed rate are higher.

In the halo ketones, it is of note that 2-chlorocyclohexanone and 2-bromocholestan-3-one are less reactive than cyclohexanone. In the chlorocyclohexanone the halogen is mainly equatorial[19] in the equilibrium mixture, and in the 2-bromocholestan-3-one it is known that bromine is α-equatorial. In both cases the dipole of the halogen and the carbonyl are in the same plane and this makes more difficult the polarization of the carbonyl with development of a positive charge on the carbonyl carbon. As a consequence these two halo ketones have a lower rate than cyclohexanone. A second bromine atom increases 26 times the rate in comparison with the monobromo ketone. This second bromine is axial and the increase in rate should be due to participation of the bromine atom and stabilization of the positive charge by formation of a bromonium ion.

Cholestan-3-one has a rate similar to that of cyclohexanone. The keto group at C-17 is oxidized at a rate that can be compared with the one of camphor and is in agreement for a 2,2,3-trisubstituted cyclopentanone. The C-20 keto group is still less reactive than the C-17 keto group.

The obtained results allow us to establish the following order of oxidation for keto steroids: 3-keto > 17-keto > 20-keto.[21]

Acknowledgment.—The authors thank Dr. A. Cross for improving the writing of the manuscript, and Dr. K. Kopecky for helpful comments.

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[13] L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).

[14] E. L. Bennett and C. Nieman, *J. Am. Chem. Soc.*, **74**, 5076 (1954).

[15] H. L. Goering and L. L. Simons, *ibid.*, **79**, 6270 (1957).

[16] D. S. Noyce and B. N. Bastian, *ibid.*, **82**, 885, 1246 (1960).

[17] D. S. Noyce and B. R. Thomas, *ibid.*, **79**, 755 (1957).

[18] Some explanations could be given about the influence of these remote substituents on the control of reaction rate, *e.g.* conformational, alkyl participation, etc. We feel that more work is necessary to obtain conclusive evidence about the 1,4-interaction of cyclohexyl compounds.

[19] K. Kozima and Y. Yamanouchi, *J. Am. Chem. Soc.*, **81**, 4159 (1959).

[20] R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *ibid.*, **74**, 2828 (1952).

[21] A similar order has been found for the reduction of these ketones with sodium borohydride [J. L. Mateos, *J. Org. Chem.*, **24**, 2034 (1959)] and a similar trend is observed for the integrated absorption area of the carbonyl in their infrared spectra [R. Cetina and J. L. Mateos, *ibid.*, **25**, 704 (1960)].

Synthesis of α-(Ferrocenylmethyl) Ketones by the Enamine Method[1]

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Many aldehydes and ketones can be α-alkylated *via* C-alkylation of their enamines.[3-6] N-Alkylation of enamines, which occurs to a considerable extent when simple alkyl halides are used as alkylating agents, leads to ultimate recovery of starting carbonyl compounds and is, of course, undesirable. The desired C-alkylation occurs to the exclusion of N-alkylation when the alkylating agents are reactive halides like allyl halides, benzyl halides and α-halo esters, or conjugated olefins like acrylonitrile and acrylic esters. By analogy with benzyl halides, the ferrocenylmethyl

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[2] To whom inquiries should be addressed at the Department of Chemistry, Florida Atlantic University, Boca Raton, Fla.

[3] G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

[4] G. Stork and H. Landesman, *ibid.*, **78**, 5128 (1956).

[5] G. Stork, Abstracts of Sixteenth National Organic Chemistry Symposium, Seattle, Wash., June, 1959, pp. 44-52.

[6] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

halides should bring about exclusive or at least predominant C-alkylation of enamines. The net result would be the introduction of the ferrocenylmethyl group into the α-position of carbonyl compounds. However, attempts at the synthesis and isolation of ferrocenylmethyl halides have so far failed, although the chloride has apparently been obtained in solution.[7] (Ferrocenylmethyl)trimethylammonium iodide has often served as ferrocenylmethylating agent in place of the missing ferrocenylmethyl halides.[8–15] We now report the successful use of this quaternary ammonium salt in the synthesis of 2-(ferrocenylmethyl)cyclopentanone and 2-(ferrocenylmethyl)cyclohexanone by the alkylation of the pyrrolidine enamines of cyclopentanone and cyclohexanone, respectively. To our knowledge this work represents the first instance of a quaternary ammonium salt being used in enamine alkylation. N-Ferrocenylmethylation of the enamines did not appear to take place, since no N-(ferrocenylmethyl)-pyrrolidine could be isolated after hydrolytic work-up. However, variable amounts of the latter substance were obtained along with reduced yields of the desired ketones, whenever the alkylation solvent used was not dry. The explanation lies in hydrolytic cleavage of a portion of the enamine in the wet solvent and subsequent reaction of the quaternary ammonium salt with pyrrolidine, a reaction which could be independently demonstrated. Other examples of the ferrocenylmethylation of secondary amines by the quaternary ammonium salt have been reported.[13]

The ultraviolet-visible spectra of the two α-(ferrocenylmethyl) ketones contained no evidence for intramolecular interaction between iron and the carbonyl group in the respective side chains. A broad band tending to eclipse the ferrocene spectrum in the 300–400-mμ region has been observed with ferrocene derivatives where interaction (charge transfer) between iron and a group in a side chain is very plausible.[14] The spectra of the ketones did not contain such a band.

Experimental[16]

2-(Ferrocenylmethyl)cyclohexanone.—A solution of N-cyclohexenylpyrrolidine[17,18] (3.10 g., 0.0226 mole) and (ferrocenylmethyl)trimethylammonium iodide[19] (4.50 g., 0.0117 mole) in 75 ml. of anhydrous acetonitrile (distilled over phosphorus pentoxide) was refluxed under a stream of nitrogen for 24 hr. By the end of the refluxing period trimethylamine evolution had practically ceased. New acetonitrile had to be added from time to time to compensate for losses caused by entrainment with nitrogen gas. For hydrolytic work-up the red-brown reaction mixture was treated with 75 ml. of water and 7.5 ml. of 6 *N* hydrochloric acid and refluxed for 3 hr. More water then was added. The brown oil which settled to the bottom solidified in the refrigerator. The crude product had m.p. 70–74° and weighed 3.04 g. (88%). After recrystallization from aqueous ethanol the substance consisted of yellow crystals, m.p. 73–75°. It is readily soluble in common organic solvents and insoluble in water. The ultraviolet-visible spectrum shows a shoulder at 328 mμ (log ϵ 2.13), a minimum at 368 (1.70), and a maximum at 436 (2.13). In comparison, the spectrum of simple ferrocene exhibits a minimum at 305 mμ (log ϵ 1.50), a maximum at 328 (1.84), a minimum at 364 (1.27), and a maximum at 432 (2.06). The ketone lacks the minimum at 305 mμ and has a shoulder rather than a peak at 328 mμ because the high wave-length side of the carbonyl absorption band falls in that region (the peak for the ketonic carbonyl group is generally somewhat below 300 mμ). The infrared spectrum (KBr pellet) of the ketone shows carbonyl absorption at 5.8 μ and possesses the various absorption bands of ferrocenes with an unsubstituted ring.

Anal. Calcd. for $C_{17}H_{20}FeO$: C, 68.93; H, 6.81; Fe, 18.86; O, 5.40. Found: C, 68.96, 68.95; H, 6.80, 6.86; Fe, 18.9; O, 5.50.

When the aqueous solution, after removal of the ketone, was made alkaline, a small quantity of brownish-black gummy solid precipitated. This material, other than being soluble in dilute mineral acid, did not resemble the N-(ferrocenylmethyl)pyrrolidine described below.

N-(Ferrocenylmethyl)pyrrolidine.—If the reaction of N-cyclohexenylpyrrolidine with (ferrocenylmethyl)trimethylammonium iodide was carried out in acetonitrile which had not been dried, the desired ketone was formed in reduced yield. Furthermore, when the aqueous solution after removal of the ketone was made alkaline, a quantity of N-(ferrocenylmethyl)pyrrolidine was obtained as yellow-brown precipitate. After recrystallization from aqueous ethanol, the crystals were glossy yellow and had m.p. 52–54°. The substance is soluble in common organic solvents and in dilute mineral acids and virtually insoluble in water. The ultraviolet-visible spectrum shows a minimum at 308 mμ (log ϵ 1.82), a maximum at 328 (1.95), a minimum at 364 (1.46), and a maximum at 440 (2.07), and thus closely resembles the spectrum of ferrocene. The infrared spectrum is in accord with the assigned structure.

Anal. Calcd. for $C_{15}H_{19}FeN$: C, 66.93; H, 7.10; Fe, 20.76; N, 5.21. Found: C, 67.29; H, 7.05; Fe, 21.3; N, 5.10.

Direct reaction of (ferrocenylmethyl)trimethylammonium iodide with pyrrolidine produced the identical compound.

2-(Ferrocenylmethyl)cyclopentanone.—This synthesis resembled that of the corresponding cyclohexanone except that N-cyclopentenylpyrrolidine[20] was used as the enamine. The crude ketone was first obtained as an oil which crystallized after standing for several days in the refrigerator. The melting point of the crude ketone was 39–42° and the yield was 54%. On attempted recrystallization, only oil was obtained. The substance is readily soluble in organic solvents and insoluble in water. The ketone in its oily form is subject to gradual self-condensation (probably of the aldol type) as evidenced by the fact that after prolonged standing the oil is no longer completely soluble in ether; the insoluble portion is an amorphous solid. The ultraviolet-visible spectrum of the crude ketone shows a minimum at 374 mμ (log ϵ 2.13) and a maximum at 436 mμ (log ϵ 2.26). The infrared spectrum (KBr pellet) shows a carbonyl peak at 5.8 μ as well as various absorption peaks associated with ferrocenes having an unsubstituted ring.

The ketone was converted into the oxime, m.p. 154–156° after three recrystallizations from aqueous ethanol, and into the semicarbazone, m.p. 218–228° dec. after two recrystallizations from aqueous ethanol. The semicarbazone is an especially advantageous derivative, since it is formed quantitatively and is recrystallizable with little loss.

Anal. Calcd. for $C_{17}H_{21}FeN_3O$: C, 60.14; H, 6.23; Fe, 16.46; N, 12.44. Found: C, 60.90; H, 6.32; Fe, 16.25; N, 11.87.

When the aqueous solution left after removal of 2-(ferrocenyl-

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[7] K. Schlögl, *Monatsh. Chem.*, **88**, 601 (1957).

[8] G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *J. Chem. Soc.*, 650 (1958).

[9] J. M. Osgerby and P. L. Pauson, *ibid.*, 656 (1958).

[10] A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and Yu. A. Ustinyuk, *Dokl. Akad. Nauk SSSR*, **124**, 331 (1959).

[11] A. N. Nesmeyanov, E. G. Perevalova, Yu. A. Ustinyuk, and L. S. Shilovtseva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 524 (1960).

[12] A. N. Nesmeyanov, E. G. Perevalova, and L. S. Shilovtseva, *ibid.*, 1982 (1961).

[13] A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and V. D. Tyurin, *ibid.*, 1997 (1962).

[14] M. C. Mathews and T. I. Bieber, Abstracts, 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov., 1962, p. 73.

[15] P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 2990 (1963).

[16] Melting points are uncorrected. For determination of ultraviolet-visible spectra, the samples were dissolved in Spectro Grade acetonitrile. Microanalyses were carried out by K. W. Zimmermann, University of Melbourne, Australia.

[17] M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.*, **74**, 3627 (1952).

[18] S. Hünig, E. Benzing, and E. Lücke, *Chem. Ber.*, **90**, 2833 (1957).

[19] J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957); modified synthesis by Osgerby and Pauson.[9] The synthesis was further modified by the use of metaphosphoric acid, in place of orthophosphoric acid, in the condensation of ferrocene with N,N,N′,N′-tetramethyldiaminomethane and by a longer reaction time (72 hr.). This led to improved conversions.

[20] G. Opitz, H. Mildenberger, and H. Suhr, *Ann. Chem.*, **650**, 115 (1961).

methyl)cyclopentanone was made basic, a gummy solid was obtained from which no N-(ferrocenylmethyl)pyrrolidine was isolable. If undried solvent was used as solvent in the enamine alkylation, some N-(ferrocenylmethyl)pyrrolidine was obtained at this stage.

Biindolyls. III. Substituted 2,3'-Biindolyls from 3-Arylacetylindoles[1,2]

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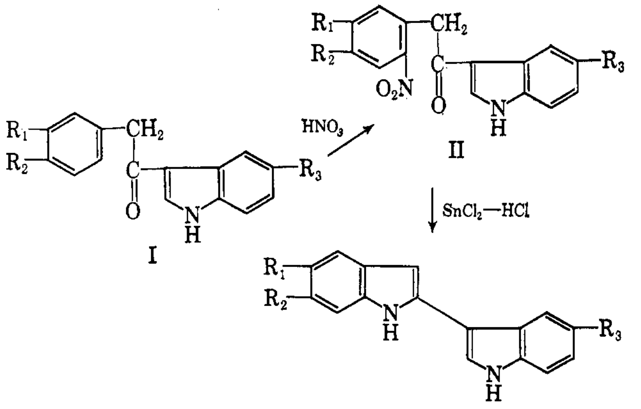
For reasons cited in an earlier paper[4] we have been seeking broadly applicable methods for the synthesis of substituted 2,3'-biindolyls. Although low yields of such compounds have been obtained on reduction of 2-(3-indolyl)-3H-pseudoindol-3-ones,[2] the more successful synthesis of 5,6-dimethoxy-2,3'-biindolyl (IIIa) by reductive cyclization of 3-(4,5-dimethoxy-2-nitrophenylacetyl)indole (IIa)[4] appeared to be more promising as a potentially general route to the desired class of compounds. It has now been found that the accessibility of the 3-(*o*-nitrophenylacetyl)indoles (II) required as starting materials is sharply limited, a deficiency which has confined the over-all method to a few special cases summarized by the sequence of formulas (I to III, a–d).

In this reaction sequence, the crucial introduction of the nitro group at the necessary *ortho* position of the phenyl ring is dependent on the relative reactivities of aryl and indolyl moieties. Although fortuitously favorable in the cases cited (60–95% yield of II), the balance is delicately controlled by all substituents as shown by unsuccessful attempts to nitrate 19 additional 3-arylacetylindoles,[5] most of which were expected to yield the required 3-(*o*-nitroarylacetyl)indoles. For example, 3-methoxy-, 3,4-dichloro-, 3,4-dimethyl-, 2-chloro-3,4-dimethoxy-, 5-chloro-3,4-dimethoxy-, and 2-chloro-4,5-dimethoxyphenylacetylindoles, as well as their 5-bromoindole analogs, were all recovered unchanged from nitric–acetic acid media at room temperature. At higher temperatures, extensive decomposition occurred in all cases. The 2-methylindole analogs of Ia–d, although easily attacked by the same nitrating medium at room temperature, also gave no well-defined mononitration products.



I

II

III

	R_1	R_2	R_3
a	MeO	MeO	H
b	MeO	MeO	Br
c	O-CH₂-O		H
d	O-CH₂-O		Br

Reduction of the nitro ketones (IIb–d) with stannous chloride and hydrochloric acid in glacial acetic acid easily afforded the corresponding 2,3'-biindolyls (IIIb–d), albeit in yields of only 10–47%. All of these 2,3'-biindolyls showed ultraviolet absorption spectra similar to that of 2,3'-biindolyl, formed yellow solutions with dilute ethanolic hydrogen chloride, and gave stable blue "rosindoles" with Ehrlich's reagent, thus confirming their structural assignments, as well as those of the precursor nitro compounds (II). A more detailed structure proof for IIa has already been presented.[4]

Experimental[6]

Acylation of Indoles. General Procedure.—A solution of 0.11 mole of indole (or 5-bromoindole) in 50 ml. of anhydrous benzene was added dropwise during 10 min. to a vigorously stirred solution of 0.117 mole of phenylmagnesium bromide, prepared in the usual way, in 100 ml. of anhydrous ether. The resulting mixture was refluxed for 2 hr., then cooled to −10° in a Dry Ice–methanol bath. A solution of 0.100 mole of the arylacetyl chloride in 40 ml. of benzene was then added dropwise during 45 min. while the temperature was maintained at −8 to −10°. The cooling bath was removed; the mixture was stirred an additional 30 min., then hydrolyzed by addition of 50 ml. of 10% aqueous ammonium chloride. The resulting solid product was collected by filtration, washed several times with ether, then air-dried. The products so obtained are described individually in the following paragraphs.

3-(3,4-Dimethoxyphenylacetyl)-5-bromoindole (Ib).—The reaction of 5-bromoindolylmagnesium bromide and homoveratroyl chloride[4] gave this product directly on hydrolysis of the reaction mixture in 37% yield. Recrystallization from 95% ethanol afforded white needles, m.p. 228–230°, infrared (μ), 3.16 (N-H) and 6.06 (C═O).

Anal. Calcd. for $C_{18}H_{16}BrNO_3$: C, 57.76; H, 4.31; N, 3.74. Found: C, 57.89; H, 4.60; N, 3.67.

3-(3,4-Methylenedioxyphenylacetyl)indole (Ic).—Reaction of indolylmagnesium bromide and 3,4-methylenedioxyphenylacetyl chloride[7] yielded 21 g. (95%) of 1,3-di(3,4-methylenedioxyphenylacetyl)indole, which was recrystallized from *n*-propyl alcohol to give white needles, m.p. 145–146°, infrared (μ), 5.76 and 5.95 (C═O).

Anal. Calcd. for $C_{26}H_{19}NO_6$: C, 70.74; H, 4.34; N, 3.17. Found: C, 70.95; H, 4.71; N, 3.14.

Two grams of this product was refluxed for 5 min. with a solution of 5 ml. of 10% sodium hydroxide in 20 ml. of 95% ethanol. The resulting hot solution was diluted with 10 ml. of water, filtered, and allowed to cool to room temperature. The resulting crop of crystals was collected, washed with water, then recrystallized from 95% ethanol to give 1.1 g. (88% yield) of Ic, m.p. 194–196°, infrared (μ), 3.01 (N-H) and 6.12 (C═O).

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.02. Found: C, 73.25; H, 4.80; N, 4.94.

3-(3,4-Methylenedioxyphenylacetyl)-5-bromoindole (Id).—Reaction of 5-bromoindolylmagnesium bromide and 3,4-methylenedioxyphenylacetyl chloride yielded 22.8 g. of a crude white solid

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[1] This investigation was supported by Research Grant C-4425 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

[2] Part II: T. E. Young and D. S. Auld, *J. Org. Chem.*, **28**, 418 (1963).

[3] Abstracted from the Ph.D. dissertation of M. F. M., Lehigh University, 1963.

[4] T. E. Young, *J. Org. Chem.*, **27**, 507 (1962).

[5] Syntheses and properties of these compounds will be reported elsewhere.

[6] Melting points are corrected. Infrared spectra were determined in potassium bromide on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were run on a Beckman DK-2A instrument. Indole and 5-bromoindole were obtained from Aldrich Chemical Co., Milwaukee, Wis.

[7] C. Mannich and O. Walther, *Arch. Pharm.*, **265**, 7 (1927); *cf. Chem. Zentr.*, 1, 1479 (1927).