anol and from benzene–petroleum ether (b.p. 68–70°) when it formed clear white prisms melting at 169.5–171.5°.

Anal. Calcd. for $C_{21}H_{21}NO_7$: C, 63.2; H, 5.30; N, 3.51. Found: C, 63.1; H, 5.46; N, 3.41.

The 2,4-dinitrophenylhydrazone of XVI was identical with those derived from XIV and XV and melted at 177.5–178°, alone or when mixed with these. An attempt was made to prepare a semicarbazone of XVI, but the product of this reaction was XV, m.p. and mixed m.p. 108.5–110°. Action of potassium acetate (2 g., 0.02 mole) in methano (50 cc.) upon XVI (1 g.) converted it into XV. The solution was refluxed for one hour, then poured into water, and extracted with ether (four 50-cc. portions). The combined extracts were dried (magnesium sulfate), the solvent was removed, and the residue was crystallized from petroleum ether (100 cc., b.p. 68–70°). It weighed 0.57 g. (65%) and melted at 107–108°, alone or when mixed with XV.

MINNEAPOLIS 14, MINNESOTA

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Cyclopropanes. XI.[1] Pyrones from Nitrocyclopropyl Ketones

BY LEE IRVIN SMITH AND RALPH E. KELLY[2]

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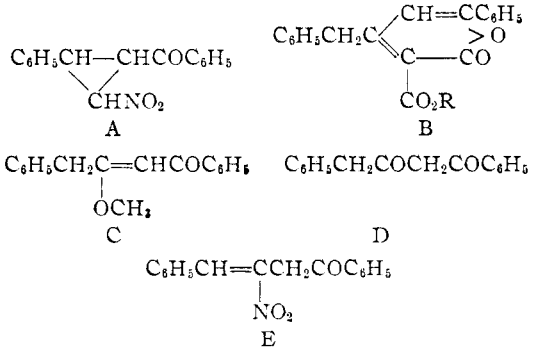
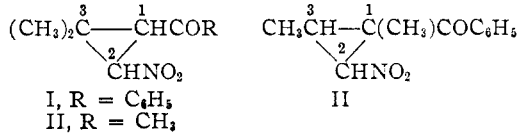
Three nitrocyclopropyl ketones, of two different types—I and II having no hydrogen atoms attached in the 3-position, and III having none in the 1-position—have been subjected to the action of sodio malonic esters. All three of the cyclopropanes were converted into α-pyrone esters by action of this reagent. The reaction of II, which differs from I only in that it is a methyl ketone instead of a phenyl ketone, was complicated because of the presence of the aliphatic ketone group. Because of this, II gave more products than did I or III, and the yield of pyrone from II was low. This pyrone ester V was therefore synthesized *via* an independent sequence of reactions, starting with isopropylacetylene. Formation of pyrone esters from cyclopropanes I and II is consistent with the assumption that an acetylenic ketone is involved as an intermediate, but formation of such a pyrone ester from cyclopropane III cannot be reconciled with this assumption, unless the further assumption is made that the intermediate β,γ-acetylenic ketone XVIII would add malonic ester in one direction only. There is, *a priori*, no reason for assuming that this would be the case.

In the previous paper[1] the action of sodio malonic esters upon the nitrocyclopropyl ketone A was examined; it was shown that the product was the α-pyrone ester B. Moreover, all but one of the products derived from A by action of alkali according to the sequence proposed by Smith and Engelhardt[3]—the enol ether C of the 1,3-diketone D, the diketone D itself, and the unsaturated nitro ketone E—were examined, and none of these was converted, by action of sodio malonic esters, into the α-pyrone B.



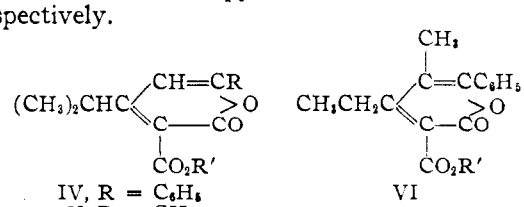
The number of nitrocyclopropyl ketones examined in the earlier work[1,4] was small, and moreover they were all of the same type as A, in which each of the carbon atoms of the ring held one hydrogen atom. Because this conversion of nitrocyclopropanes into pyrones is an important reaction which must be taken into account in formulating any comprehensive mechanism for the reaction between nitrocyclopropyl ketones and bases, the study has been extended to include nitrocyclopropyl ketones differing from A in the location of the hydrogen atoms attached to the ring. Three nitrocyclopropyl ketones—I, II, III—were selected for the study. These are of two types: I and II possess no hydrogen atom on the number 3 carbon atom of the ring, but have one on each of the other two carbon atoms; III has no hydrogen atom on the number 1 carbon atom of the ring, but has one on each of the other two carbon atoms. I differs from II only in the nature of the acyl group;



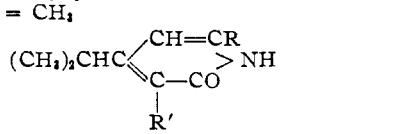
I, R = C_6H_5
II, R = CH_3

in one case this is benzoyl, and in the other case, acetyl. The latter compound was included in the study so that the series under examination would comprise not only aromatic, but at least one purely aliphatic, nitrocyclopropyl ketone.

The nitrocyclopropyl ketones I, II and III, when subjected to the action of sodio malonic ester, were converted into the α-pyrone esters IV, V and VI, respectively.



IV, R = C_6H_5
V, R = CH_3



VII, R = C_6H_5
VIII, R = CH_3

(1) Paper X, L. I. Smith and R. E. Kelly, THIS JOURNAL, **74**, 3300 (1952).

(2) Abstracted from a thesis by Ralph E. Kelly, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, August, 1951. du Pont Fellow, 1950–1951.

(3) L. I. Smith and V. A. Engelhardt, THIS JOURNAL, **71**, 2671, 2676 (1949).

(4) E. P. Kohler and L. I. Smith, *ibid.*, **44**, 624 (1922).

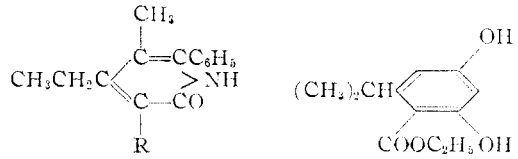
Pyrone IV (R′ = C_2H_5) was produced from I in 56% yield; this pyrone was a viscous oil which could not be induced to crystallize. Mild hydrolysis converted IV into the pyrone acid (IV, R′ = H) which was characterized as the *p*-phenylphenacyl ester. Action of methanolic ammonia upon the ester IV was accompanied by hydrolysis and decarboxylation; the product was the pyridone VII (R′ = H). It was hoped that I could be converted into the β-nitro-β,γ-unsaturated ketone X by a series of reactions analogous to that described in the previous paper[1] and that, in this case, the phenyl group in the β,γ-unsaturated ketone X might exert some influence and hence X, in the

$(CH_3)_2CBrCHCH_2COC_6H_5$ $(CH_3)_2C{=}CCH_2COC_6H_5$
NO_2 NO_2
IX X

$(CH_3)_2CHC{=}CHCOC_6H_5$
NO_2
XI

presence of bases might undergo a rearrangement into the α,β-ketone XI. If so, action of malonic ester upon XI might produce the pyrone IV and so provide some support for the assumption[3] that nitro ketones such as XI are likely intermediates in the reaction between bases and nitrocyclopropyl ketones. Action of hydrogen bromide in acetic acid converted I into IX, but all efforts to convert IX into an unsaturated nitro ketone failed.

Pyrone VI (R′ = C_2H_5) was formed from III in 40% yield. This pyrone ester was hydrolyzed to the pyrone acid VI (R′ = H) which was characterized as the *p*-phenylphenacyl ester. Decarboxylation of the pyrone acid produced the parent pyrone. Action of methanolic ammonia upon the pyrone ester produced an inseparable mixture of pyridones XIIa and XIIc. The mixture was subjected to mild hydrolysis and the pyridone acid XIIb was thus separated from XIIc. Decarboxylation of XIIb produced XIIc.



XIIa, R = $COOC_2H_5$
b, R = COOH
c, R = H

XIII

$(CH_3)_2CHC{=}CHCOCH_3$
$CH(COOC_2H_5)_2$
XIV

The reaction between the aliphatic nitrocyclopropyl ketone II and sodio malonic ester was much more complex than the analogous reactions of the aromatic ketones I and III. Although the pyrone ester V (R = C_2H_5) was formed, the yield was very small and the bulk of the product consisted of the ethyl enol ether of the 1,3-diketone and a substance (about 30%) isomeric with the pyrone ester and which has been formulated as 4-carbethoxy-5-isopropylresorcinol (XIII). The pyrone V and the resorcinol XIII probably arise from common precursors—first the nitro ketone analogous to XI, then the malonic ester XIV which can undergo cyclization either to the pyrone or to the resorcinol. However, this substance could not be definitely identified; all attempts to prepare a solid dibenzoate or dinitrobenzoate of XIII were unsuccessful. The substance XIII gave an acid upon hydrolysis, but when this was decarboxylated, the product was a dark oil which likewise could not be converted into solid esters.[5] In order to be certain as to the structure of the pyrone ester V, this was synthesized *via* an independent sequence of reactions. Isopropylacetylene XV was synthesized from methyl iso-

$(CH_3)_2CHC{\equiv}CH$ $(CH_3)_2CHC{\equiv}CCHOHCH_3$
XV XVI

$(CH_3)_2CHC{\equiv}CCOCH_3$
XVII

propyl ketone by the method of Ivitsky.[6] The acetylene was converted into the Grignard reagent and the latter was allowed to react with acetaldehyde, giving the carbinol XVI. Oxidation of the carbinol by action of chromic acid[7] produced the ketone XVII which reacted with sodio malonic ester[8] to produce the α-pyrone ester V (R′ = C_2H_5) melting at 71–71.5° alone or when mixed with V obtained from the cyclopropane II. Hydrolysis of the pyrone ester V according to the method of Bickel[9] yielded an oil which could not be crystallized, but action of methanolic ammonia upon V resulted in loss of the carbethoxyl production of the pyridone VIII (R′ = H).

This work, together with that described in the previous paper[1] has shown that nitrocyclopropyl ketones of types A, I, II and III all give α-pyrone esters when subjected to the action of sodio malonic ester. It was pointed out previously[3] that the mechanism for the reaction between nitrocyclopropyl ketones and bases, originally proposed by Smith and Kohler[4] and in which an acetylenic ketone is an assumed intermediate, although able to account for the behavior of types A, I and II, cannot account for the behavior of type III. In this case, the acetylenic ketone must of necessity be β,γ-unsaturated (XVIII). Such a ketone, if

$CH_3C{\equiv}CCH(CH_3)COC_6H_5$ $CH_2CH{=}CCH(CH_3)COC_6H_5$
B
XVIII XIX

an intermediate, would have to add a base (CH(COOR)$_2$, OCH_3, etc.) preferentially so as to give products of type XIX for only in this way would the reaction lead to the products actually obtained from III. Recently a new mechanism for this reaction was proposed[3] and in the previous paper it was shown that intermediates of types C, D and E were not precursors of the α-pyrones. The one type of intermediate not tested was the β-nitro-α,β-unsaturated ketone of type XI. In an attempt

(5) Since our work was completed, Brown, Johnson, Robertson and Whalley, *J. Chem. Soc.*, 2020 (1951), have synthesized 5-isopropylresorcinol. This compound melts at 110°, boils at 120° (0.15 mm.), and is readily converted into a di-*p*-nitrobenzoate melting at 183°.

(6) M. P. Ivetsky, *Bull. soc. chim.*, [4] **35**, 357 (1924).

(7) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(8) E. P. Kohler, THIS JOURNAL, **44**, 379 (1922).

(9) C. L. Bickel, *ibid.*, **72**, 1022 (1950).

to prepare a nitro ketone of this type, phenylglyoxal was condensed with nitroethane. The product, obtained in poor yield was the hydroxy

$$C_6H_5COCHCHCH_3$$
$$\quad\quad\;|\quad\;|$$
$$\quad\quad OR\;NO_2$$

XX, R = H
XXI, R = Ac

compound XX. This was converted in good yield into the acetate XXI, but the latter could not be converted into the unsaturated nitro ketone by the method of Nightingale and Janis.[10]

Experimental Part[11]

1-Benzoyl-2-nitro-3,3-dimethylcyclopropane (I) and Derivatives.—The cyclopropane I, m.p. 65.5–66.5°, was prepared *via* the sequence of reactions previously described,[3] but the α,β-unsaturated ketone, isopropylideneacetophenone was prepared by action of diphenyl cadmium upon senecioyl chloride, rather than *via* a Friedel-Crafts reaction. The new method gives a superior product, and in much better yield.

Isopropylideneacetophenone.—Anhydrous cadmium chloride[12] (170 g., 0.93 mole) was added in five portions and with stirring to a solution of phenylmagnesium bromide (bromobenzene, 290 g., 1.85 moles; magnesium, 45 g., 1.85 moles) in ether (600 cc.) at 0°. The suspension was refluxed for one hour, then ether was removed until a thick paste remained. Dry benzene (400 cc.) was added and distillation was continued until all the ether was removed. Additional benzene (200 cc.) was added, the suspension of diphenylcadmium was cooled (10°) and to it was added, dropwise and with vigorous stirring, a solution of senecioyl chloride (100 g., 0.85 mole) in dry benzene (200 cc.) at such a rate that the temperature did not exceed 37°. The mixture was poured into iced sulfuric acid, the organic layer was removed, and the aqueous layer was extracted with benzene (100 cc.). The combined organic layers were washed successively with water (500 cc.), aqueous sodium carbonate (5%), water, and saturated aqueous sodium chloride and then dried (sodium sulfate). The solvent was removed and the residue, distilled through a column (6″) packed with glass helices, gave a distillate (125 g., 94%) boiling at 86–94° (0.9–1.3 mm.), and having $n^{25}D$ 1.5620. This product contained a little biphenyl.

3-Carbethoxy-4-isopropyl-6-phenyl-α-pyrone (IV, R′ = C_2H_5).—Sodium (3.68 g., 0.16 gram atom) was added to a solution of ethyl malonate (25.6 g., 0.16 mole) in dry ethanol (300 cc.) in a flask equipped with a soxhlet extractor. The cyclopropane I (10 g., 0.046 mole) was placed in the soxhlet cup and the solution was refluxed for 1.5 hours. Acetic acid (9.6 g., 0.16 mole) was added, ethanol was removed under reduced pressure, water was added, and the mixture was extracted with ether (three 80-cc. portions). The combined extracts were washed with water, dried (magnesium sulfate), and the solvent was removed. Excess ethyl malonate was removed by distillation under 0.2 mm.; and the dark residue was then distilled from a "sausage" flask. The product (7.25 g., 56%) was a reddish oil boiling at 140–160°, which could not be crystallized. A sample boiling at 160° (0.005 mm.) was analyzed.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.33. Found: C, 70.7; H, 6.25.

3-Carboxy-4-isopropyl-6-phenyl-α-pyrone (IV, R′ = H).—Aqueous sodium hydroxide (0.1 *N*, 39.8 cc.) was added dropwise (30 minutes) to a solution of the above pyrone ester (1.07 g., 0.004 mole) in acetone (50 cc.).[9] The mixture was allowed to stand for an hour, then was poured into water and extracted with ether (three 100-cc. portions). The organic layers were discarded; the aqueous phase was acidified with dilute hydrochloric acid and extracted with ether (three 50-cc. portions). The combined extracts were dried (magnesium sulfate), the solvent was removed under reduced pressure, and the residual pasty solid was dissolved in benzene (30 cc.). The solution, when diluted with petroleum ether (100 cc., b.p. 68–70°) deposited thick yellow prisms (0.83 g., 85%) melting at 154–158°. The analytical sample, crystallized three times from benzene–petroleum ether and twice from aqueous methanol, melted at 158–159°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.46. Found: C, 69.6; H, 5.43.

The *p*-phenylphenacyl ester, crystallized several times from benzene–petroleum ether, melted at 189–190°.

Anal. Calcd. for $C_{29}H_{24}O_5$: C, 77.0; H, 5.61. Found: C, 77.5; H, 5.40.

4-Isopropyl-6-phenyl-2-pyridone (VII, R′ = H).—A cold (0°) solution of the pyrone ester (IV, R′ = C_2H_5) (2.05 g., 0.007 mole) in dry methanol (25 cc.) was saturated with ammonia gas. The flask was tightly stoppered and allowed to stand at room temperature for 20 hours. The ammonia and the solvent were removed in a current of dry air and the residual oil was extracted with petroleum ether (100 cc., b.p. 68–70°). The extract was evaporated and the residue was crystallized successively from aqueous ethanol (30%) and petroleum ether. The fine needles melted at 127–128.5°.

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.8; H, 7.09; N, 6.57. Found: C, 78.9; H, 7.11; N, 6.32.

γ-Bromo-β-nitroisocaprophenone (IX), m.p. 112.5–114°, was prepared from the cyclopropane I as described previously.[3] A solution of IX (13.2 g.) in cyclohexane (300 cc.). and pyridine (7.9 g.) was refluxed for 21 hours and then cooled (0°). The solid (IX, 3.2 g., m.p. 105–107°) was removed, the filtrate was washed successively with water, dilute hydrochloric acid, aqueous sodium bicarbonate (5%) and water, and dried (magnesium sulfate). Solvent was removed under reduced pressure; the residual oil became green on standing and deposited more IX (0.64 g.). The green oil was unsaturated toward permanganate. When distilled, the oil gave a distillate (0.7 g.) boiling at 90–103° (0.3 mm.). This light yellow oil became blue-green on standing. An attempt to prepare a semicarbazone from this oil was unsuccessful. The experiment was repeated using acetone as the solvent and triethylamine as the base. Although triethylamine hydrobromide (5.7 g., theory 7.1 g.) was formed, the filtrate from this yielded only a small amount of light yellow oil (1.36 g., b.p. 107–119° (0.9 mm.)) which became deep blue-green on standing.

1-Benzoyl-2-nitro-1,3-dimethylcyclopropane (III) and Derivatives.—The cyclopropane III, m.p. 83–84°, was prepared as previously described.[3]

3-Carbethoxy-4-ethyl-5-methyl-6-phenyl-α-pyrone (VI, R′ = C_2H_5).—The cyclopropane III (15 g., 0.07 mole) was subjected to the action of sodio ethyl malonate (ethyl malonate, 42 g., 0.27 mole; sodium, 5.75 g., 0.25 gram atom; dry ethanol, 400 cc.) as described above for the preparation of pyrone IV. The product (7 g., 40%) was a solid which, after several crystallizations from petroleum ether (b.p. 68–70°), melted at 87.0–87.7°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.33. Found: C, 71.4; H, 6.62.

3-Carboxy-4-ethyl-5-methyl-6-phenyl-α-pyrone (VI, R′ = H).—The pyrone ester VI, R′ = C_2H_5 (1 g.) when hydrolyzed as described above for hydrolysis of IV, yielded the pyrone acid (0.52 g., 58%), which, after several crystallizations from benzene–petroleum ether, melted at 162–163°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.46. Found: C, 69.9; H, 5.66.

The *p*-phenylphenacyl ester, crystallized from benzene–petroleum ether, melted at 209.8–210.8°.

Anal. Calcd. for $C_{29}H_{24}O_5$: C, 77.0; H, 5.35. Found: C, 77.0; H, 5.61.

4-Ethyl-5-methyl-6-phenyl-α-pyrone.—The above pyrone acid (0.25 g.) was heated for 15 minutes in a test-tube immersed in an oil-bath at 170°, and then at 200–220° for two hours. The cooled residue was dissolved in methanol (5 cc.) and the solution was diluted with water until cloudy and then cooled. The pyrone, after crystallization twice from aqueous methanol, melted at 75.0–75.5°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.5; H, 6.58. Found: C, 78.8; H, 6.88.

3-Carboxy-4-ethyl-5-methyl-6-phenyl-2-pyridone (XIIb).—The pyrone ester VI (1 g.) was subjected to the action of

(10) D. Nightingale and J. R. Janis, THIS JOURNAL, **66**, 353 (1944).

(11) Microanalyses by Wm. Cummings, Bob K. Davis, L. Errede, H. Turner and E. Wheeler.

(12) J. Cason, THIS JOURNAL, **68**, 2080 (1946).

saturated methanolic ammonia (25 cc.) for 18 hours at room temperature, as described above for preparation of VII. The product melted over a wide range (120–165°) and attempts to separate it into pure components by crystallization or sublimation were unsuccessful. The material was subjected to the action of boiling aqueous sodium hydroxide (25 cc., 10%) for one hour. The cooled solution was filtered and the filtrate was saturated with carbon dioxide; only a small amount of material separated. This was removed and the filtrate was acidified with dilute hydrochloric acid. The solid (0.32 g., 35%) was removed, dried, and crystallized from benzene–petroleum ether, when it melted at 240–242°.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.0; H, 5.88; N, 5.45. Found: C, 70.0; H, 6.01; N, 5.61.

4-Ethyl-5-methyl-6-phenyl-2-pyridone (XIIc).—The acid XIIb (0.13 g.) was heated at 260–270° for 1.5 hours. The product (0.1 g.) was crystallized twice from benzene–petroleum ether (b.p. 68–70°) when it melted at 213.5–214.5°.

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.8; H, 7.09; N, 6.57. Found: C, 79.1; H, 7.35; N, 6.85.

1-Acetyl-2-nitro-3,3-dimethylcyclopropane (II) and Derivatives.—The cyclopropane II, b.p. 68–71° (0.2–0.3 mm.), $n^{25.4}D$ 1.4618, was prepared as previously described.[3] A solution of II (25 g., 0.16 mole) in dry ethanol (200 cc.) was added dropwise (one hour) to a refluxing solution of sodio ethyl malonate (sodium, 11.5 g., 0.5 gram atom; ethyl malonate, 87.8 g., 0.55 mole) in dry ethanol (800 cc.). Refluxing was continued for an hour; the cooled mixture was acidified with acetic acid (30 g., 0.5 mole) and ethanol was removed under reduced pressure. The residue was diluted with water (1 l.) and extracted with ether (three 300-cc. portions). The combined extracts were washed with aqueous sodium bicarbonate, then with water, dried (magnesium sulfate), and the solvent was removed under reduced pressure. The black, residual oil, when distilled, gave the following fractions: A, 27 g., b.p. 40–50° (0.1 mm.), $n^{26.5}D$ 1.4189, recovered ethyl malonate; B, 5 g., b.p. 50–68° (0.1 mm.), $n^{26.5}D$ 1.4450, probably the ethyl enol ether $(CH_3)_2CHC(OC_2H_5)=CHCOCH_3$; C, 6 g., b.p. 115–125° (1 mm.), $n^{26.5}D$ 1.4962; D, a viscous, black residue.

Fraction C was analyzed.

Anal. Calcd. for $C_{12}H_{16}O_4$ (V, R′ = C_2H_5, or XIII): C, 64.3; H, 7.19. Found: C, 65.7; H, 8.02.

Fraction D was distilled from a sausage flask; the distillate E (11.9 g.) boiled at 145–160° (0.01 mm.). A solution of E in petroleum ether (b.p. 30–60°), when cooled in a refrigerator, deposited a solid which, after several crystallizations from petroleum ether (b.p. 68–70°) and from aqueous ethanol, formed white needles melting at 45.5–46°. This material was saturated toward permanganate, and gave a deep violet-red color with ferric chloride. This substance was probably 4-carbethoxy-5-isopropylresorcinol (XIII), although attempts to prepare a dibenzoate or a di-3,5-dinitrobenzoate were unsuccessful.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.19. Found: C, 64.2; H, 7.59.

The mother liquor from the crystallization of XIII, when further cooled, deposited a second solid, which, when crystallized from petroleum ether (b.p. 30–60°) melted at 69–70°, alone or when mixed with synthetic 3-carbethoxy-4-isopropyl-6-methyl-α-pyrone (V) (see below).

In one experiment, the residue left after the removal of fraction E, when its solution in petroleum ether was cooled, deposited a solid which, after crystallization several times from petroleum ether, melted at 135–137°. This substance gave a violet-red color with ferric chloride and had the same composition as the pyrone or resorcinol. It was obtained only once and then not in sufficient amount for investigation.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.19. Found: C, 63.4; H, 6.90.

In an experiment in which sodio methyl malonate was allowed to react with the cyclopropane II in methanol, the results were essentially as described above. Fraction B, however, was identified as the methyl enol ether $(CH_3)_2CHC(OCH_3)=CHCOCH_3$ by conversion to the diketone and identification of the latter as the copper compound, m.p. 168–169°.[3]

2,2-Dichloro-4-methylpentane.—Methyl isopropyl ketone (395 g., 4.6 moles) was added dropwise (one hour) and with stirring and cooling (0°) to phosphorus pentachloride (907 g., 5.1 moles). After the solid dissolved completely, stirring was discontinued and the mixture was allowed to stand at room temperature for 17 hours. The mixture was poured into ice-water, the organic phase was removed, washed with water, dried (magnesium sulfate) and distilled. The product, a mixture of the dichloro compound and the unsaturated monochloro compound, boiled at 76–122°. This material was suitable for use in the next step; the procedure was a modification of that of Ivitsky[6] for similar chlorinations.

Isopropylacetylene (XV).—The above crude chloro compound (367 g.) was added to powdered potassium hydroxide (1.1 kg.) in an apparatus equipped with a reflux condenser connected in turn to a condenser cooled with Dry Ice–acetone. The receiver was cooled in a bath of Dry Ice, and was protected with a guard tube filled with Dehydrite. The reaction mixture was heated to 150° for seven hours; the flow of water through the reflux condenser was adjusted so that the temperature at the stillhead did not exceed 33°. The distillate was redistilled through a Stedman column; it boiled at 30° (745 mm.)[13] and weighed 40 g. The procedure is a modification of that of Ivitsky[6] for similar reactions.

5-Methyl-3-hexyne-2-ol (XVI).—The procedure of Heilbron, *et al.*,[7] was modified as follows: A solution of ethylmagnesium bromide (from magnesium, 13.4 g., 0.55 mole, and ethyl bromide, 59 g., 0.54 mole) in ether (125 cc.) was prepared in an atmosphere of nitrogen. Isopropylacetylene (40 g., 0.59 mole) in ether (50 cc.) was added rapidly (10 minutes) with stirring to the Grignard reagent, followed by dropwise (20 minutes) addition of a solution of acetaldehyde (26 g., 0.59 mole) in ether (50 cc.). The solution was stirred for two hours, and then set aside at room temperature for 18 hours. Saturated aqueous ammonium chloride (70 cc.) was added dropwise and the ether layer was removed from the solid cake. The solvent was removed under reduced pressure, and the residue was distilled. The product (27.6 g., 45%) boiled at 70–80° (39 mm.) and had $n^{25}D$ 1.4389. The analytical sample was redistilled; it boiled at 84° (50 mm.).

Anal. Calcd. for $C_7H_{12}O$: C, 75.0; H, 10.79. Found: C, 74.5; H, 11.00.

5-Methyl-3-hexyne-2-one (XVII).—The acetylenic carbinol was oxidized according to a modification of the procedure of Heilbron, *et al.*[7] An aqueous solution (50 cc.) of chromic acid (16.8 g.) and sulfuric acid (14.2 cc.) was added dropwise (two hours) to a stirred and cooled (5–10°) solution of the carbinol XVI (20.6 g., 0.18 mole) in acetone (40 cc., alcohol-free). The mixture was stirred for 30 minutes longer, poured into ice-water, and extracted with ether (three 100-cc. portions). The extracts were washed with water, dried (magnesium sulfate), and the solvent was removed under reduced pressure. The residue was distilled; the product (12.2 g., 60%) boiled at 65–68° (41 mm.) and had $n^{24}D$ 1.4321. The analytical sample was redistilled; it boiled at 74° (47 mm.).

Anal. Calcd. for $C_7H_{10}O$: C, 76.3; H, 9.15. Found: C, 76.1; H, 9.53.

The 2,4-dinitrophenylhydrazone crystallized from ethanol in orange platelets melting at 110–110.5°.

Anal. Calcd. for $C_{13}H_{14}O_4N_4$: C, 53.8; H, 4.86; N, 19.3. Found: C, 53.5; H, 5.16; N, 19.2.

3-Carbethoxy-4-isopropyl-6-methyl-α-pyrone (V, R′ = C_2H_5).—A solution of sodium ethoxide (2 cc., 5%) in dry ethanol was added to a stirred solution of the ketone XVII (5 g., 0.045 mole) and ethyl malonate (7.27 g., 0.045 mole) in dry ethanol (50 cc.) at 50°. The mixture became yellow, then red, and the temperature rose to 72°; after an hour, when the temperature had fallen to 30°, the mixture was refluxed for 30 minutes, acidified with acetic acid (0.5 cc.), and the solvent was removed under reduced pressure. The residual oil was dissolved in ether (80 cc.) and the solution was washed successively with water, aqueous sodium bicarbonate (5%) and water, and dried (magnesium sulfate). After removal of the solvent under reduced pressure, the residual pasty solid was washed with petroleum ether (30 cc., b.p. 30–60°). The slightly yellow crystals (4.94 g., 49%) melted at 69–70.5°. The cooled petroleum ether deposited a second crop (0.97 g.), making the total yield 59%. Recrystallization of the solid from benzene–petroleum ether

(13) F. Flawitzky and P. Kriloff, *Ber.*, **11**, 1939 (1878), report the b.p. as 28–29° (751 mm.).

(b.p. 30–60°) produced thick, colorless needles melting at 71.0–71.5°, alone or when mixed with this pyrone obtained from the cyclopropane II.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.19. Found: C, 64.6; H, 7.51.

The ester was subjected to hydrolysis according to the procedure of Bickel[9] but the pyrone acid (V, R′ = H) could not be obtained as a solid.

3-Carbomethoxy-4-isopropyl-6-methyl-α-pyrone (V, R′ = CH_3).—Substitution of methyl malonate for ethyl malonate in the above preparation led to the methyl ester V, R = CH_3 (34%), but this could not be obtained as a solid. It boiled at 140–146° (0.5 mm.); the analytical sample, still not pure, boiled at 127° (0.07 mm.).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.8; H, 6.71. Found: C, 63.8; H, 7.39.

4-Isopropyl-6-methyl-2-pyridone (VIII, R′ = H).—The methyl ester of the α-pyrone acid (1.4 g.) was added to a saturated solution of ammonia gas in dry methanol (25 cc.) at 0°. The flask was stoppered and set aside for 18 hours. The solvent and ammonia were removed in a current of air and the residual oil was extracted with petroleum ether (75 cc., b.p. 68–70°) and the extract, when cooled, deposited an oil. The solution was decanted from the oil and concentrated in a current of dry air. The solid (m.p. 106–109°) was removed and sublimed at 90° (0.3 mm.), when it melted at 112.5–113.5°.

Anal. Calcd. for $C_9H_{13}ON$: C, 71.5; H, 8.66; N, 9.27. Found: C, 72.0; H, 8.81; N, 9.40.

Hydrolysis and decarboxylation thus occurred when methanolic ammonia reacted with the methyl ester. This also occurred when the ethyl ester (1 g.) was subjected to the same reaction; the product (0.31 g., 45%), after crystallization from petroleum ether (b.p. 30–60°), melted at 108–110° alone or when mixed with that obtained from the methyl ester of the pyrone acid.

The ultraviolet absorption spectrum of VIII (R′ = H) (c 9.9 × 10^{-5} mole/l.) in ethanol was determined.[14]

(14) The complete curve may be found in the Ph.D. thesis of Ralph E. Kelly, ref. 2.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Cathylation (Carbethoxylation) of Steroid Alcohols

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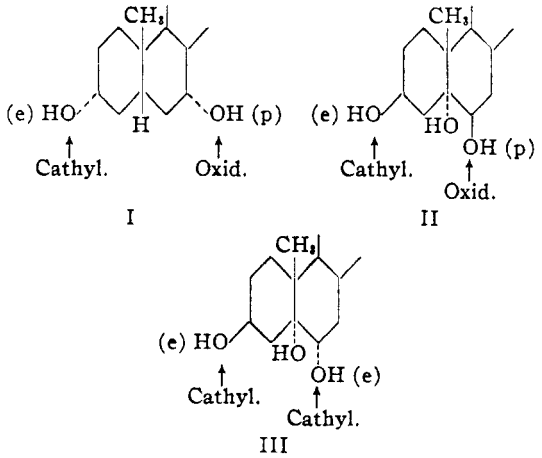
The high degree of selectivity previously observed in the reaction of methyl cholate with a large excess of ethyl chlorocarbonate to give the 3-cathyl (carbethoxyl) derivative in high yield has been interpreted by Barton in terms of the concept of polar and equatorial bonds. Study of cholestane-3β,5α,6β-triol, cholestane-3β,5α,6α-triol, cholestane-3β,7α-diol, cholestane-3β,7β-diol and androstane-3β,17β-diol has now shown that equatorial hydroxyl groups at C_6, C_7, C_{12} and C_{17} are invariably cathylated while polar hydroxyl groups are not. Less selectivity was observed in oxidations with N-bromosuccinimide. That 3α- and 3β-hydroxy derivatives of both cholestane and coprostane all afforded cathylates, if in varying yield, probably means that ring A is less rigid than the rest of the molecule. Allylic alcoholic functions, whether equatorial or polar, invariably are subject to cathylation; hence activation by a double bond overcomes hindrance effects.

In 1924 Borsche[2] reported that methyl cholate reacts with ethyl chloroformate in pyridine solution to yield the 3-carbethoxyl derivative. In recent publications we have confirmed Borsche's observation,[3] shown that methyl 3-carbethoxycholate is the exclusive reaction product even when a large excess of ethyl chloroformate is employed and can be obtained in 93% yield,[4] and reported certain other observations[4,5] indicating special advantages of the process of carbethoxylation for effecting selective acylation and for producing derivatives often characterized by excellent crystallizability and stability. It is now suggested that the useful reaction be designated cathylation and that the products be described as cathyl derivatives, analogous to tosyl, mesyl and trityl derivatives.

That methyl cholate is selectively acylated at C_3 but is oxidized with almost comparable selectivity at C_7[3] presented a perplexing problem until Barton[6] advanced a plausible interpretation based upon the general theory[7] of polar (p) and equatorial (e) bonds. In a steroid of the coprostane series, such as methyl cholate(I, assuming the chair-chair-chair conformation[6]) the 3α-hydroxyl group is equatorial and hence more vulnerable than the polar oriented



7α- and 12α-hydroxyl groups. Since in an oxidation the rate-determining step is attack of the carbon–hydrogen bond,[8] the equatorial hydrogen atom at C_7 is more vulnerable to attack than the polar hydrogen atom at C_3; that C_{12} is less vulnerable than C_7 is probably attributable to the shielding effect of the two angular methyl groups.

In the case of cholestane-3β,5α,6β-triol (II) the theory predicts selective oxidation at C_6 and selec-

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(2) W. Borsche, *Ber.*, **57**, 1620 (1924).

(3) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3935 (1949).

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(5) L. F. Fieser and S. Rajagopalan, *ibid.*, **73**, 118 (1951).

(6) D. H. R. Barton, *Experientia*, **6**, 316 (1950); see also D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

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(8) F. H. Westheimer and N. Nicolaides, *ibid.*, **71**, 25 (1949).