gummy acid fraction, which on crystallization from acetone–water yielded 66.6 mg. of 3-keto-nor-4-cholenic acid, m.p. 200–207°; methyl ester, m.p. 139–142°. A mixture of the methyl esters obtained from the monophenylethylene (III), and the diphenylethylene (V) gave no depression of the melting point.

Treatment of Cholesterol with Oxalic Acid.—A mixture of 1.0 g. of cholesterol, 4.0 g. of anhydrous oxalic acid, and 30 ml. of Dowtherm A was heated under reflux for five hours in an atmosphere of nitrogen. The Dowtherm was removed by steam distillation, and the water insoluble residue was adsorbed on 116 g. of chromatographic alumina from petroleum ether solution. Elution with petroleum ether–benzene (3:2) gave 90 mg. of material which was not further investigated. Elution with benzene–methanol (96:4) gave 727 mg. of cholesterol which after one recrystallization from 95% alcohol melted at 148–149°.

Summary

24-Phenyl-5-cholen-3β,24 diols, epimeric at C-24, have been dehydrated by anhydrous oxalic acid to give 24-phenyl-5,23-choladien-3β-ol.

24-Phenyl-4,23-choladien-3-one has been prepared and oxidized to 3-keto-nor-4-cholenic acid.

The addition of hydrogen chloride to 24-phenyl-5,23-choladien-3β-ol acetate has been studied.

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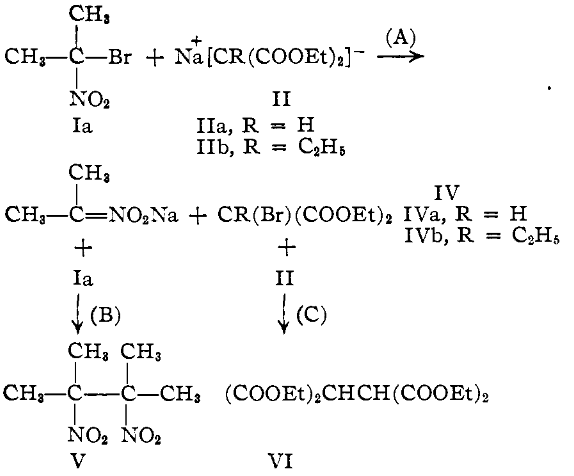
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF HOPE COLLEGE]

The Malonic Ester Reaction with 1-Halo-nitroparaffins

BY EUGENE E. VAN TAMELEN[1] AND GERRIT VAN ZYL

In view of the present availability of the nitroparaffins, the reaction of the readily prepared 1-halo-nitroparaffins with malonic ester was undertaken with the purpose of determining the effect, if any, of the highly electronegative nitro group upon the course of the reaction. In only one instance was a normal alkylation accomplished which resulted in a 1-nitroalkyl malonic ester.

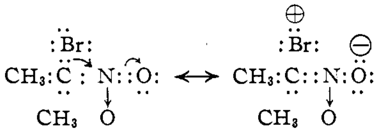
2-Bromo-2-nitropropane, Ia, was selected as a model for the bromo series, since there is no acidic hydrogen present to complicate the reaction. Upon carrying out the reaction of Ia with sodium malonic ester, IIa, under the usual conditions, two organic products were isolated: 2,3-dinitro-2,3-dimethylbutane, V, and ethane tetracarboxylic ester, VI. Since bromomalonic ester, IVa, is known to react rapidly with IIa to yield VI, IVa was postulated as an intermediate.



According to this series, one-half mole of Ia should be sufficient to convert IIa completely to VI, provided the known reaction (B) is slow.[2] It was found that the rapid addition of one-half mole of Ia to IIa gave 73% VI, with no detectable amount of V.

Since the reaction of alkyl bromomalonic esters with sodium alkyl malonic esters is not nearly as rapid as that of IVa and IIa,[3] it seemed likely that an intermediate, IVb, could be isolated if sodium ethyl malonic ester, IIb, were employed instead of IIa. Indeed, a 69% yield of IVb was obtained in this way. No matter how rapidly Ia was added to IIb, however, the formation of V could not be completely avoided—a reflection of the less rapid reaction rate of alkyl malonic esters. Increased time of addition of Ia and prolonged stirring may result in as high a yield as 30% of V.

Reaction (A) may probably be best interpreted in terms of a positively charged bromine ion. Similar reactions have been recorded in which one of the reactants possesses a halogen atom attached to the same carbon atom as one or more highly negative groups.[3] The displacement of halogen as a positive ion may be attributed to two causes: (1) the higher attraction of electrons by the nitro group as illustrated in the resonance forms



and (2) the stabilization of the resulting nitro carbanion through resonance.

The mixture of sodium salts which precipitated from the alcoholic medium during the course of the reaction was shown to consist of sodium 2-nitropropane, III, sodium bromide and sodium nitrite VII. The presence of VII along with III was unexpected, but is paralleled by the observations of Meyer[4] and Nygaard, *et al.*[5]

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[1] Present address: Harvard University, Cambridge, Massachusetts.

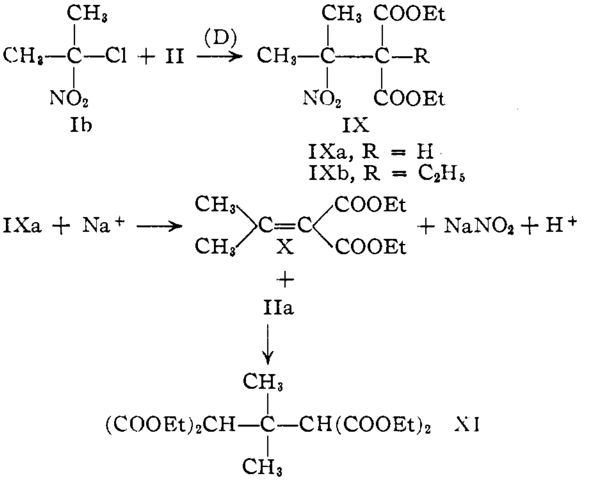
[2] L. W. Seigle and H. B. Hass, *J. Org. Chem.*, **5**, 100 (1940).

[3] C. L. Jackson and F. C. Whitmore, THIS JOURNAL, **37**, 1919 (1915).

[4] V. Meyer, *Ann.*, **175**, 88–93 (1875).

[5] E. M. Nygaard, J. H. McCracken and T. T. Noland, U. S. Patent 2,370,185.

Whereas the reaction of Ia and II proceeds *via* the positive bromine route, 2-chloro-2-nitropropane, Ib, and II result in a normal nucleophilic displacement on carbon. This is somewhat surprising in view of the foregoing, since the chlorine substituent, like the bromine, is less electronegative than the nitro group. The treatment of IIa with Ib resulted in the production of two esters: isopropylidene malonic ester, X, and isopropylidene dimalonic ester, XI



The nitro group in IXa is labilized by the acidic hydrogen in the 2-position; in the presence of strong base, sodium nitrite is easily lost with the formation of X. The addition of IIa to X yields XI.

A priori, it was not possible to determine at this point whether the series of reactions actually proceeded as outlined above; displacement of the nitro group in (D), yielding 1-chloro-1-methylethylmalonic ester, followed by loss of sodium chloride would also account for the formation of X. The question was simply solved by employing sodium ethyl malonic ester, which would yield a stable, substituted ester with no reactive hydrogen. 1-Nitro-1-methylethyl ethylmalonic ester, IXb, was obtained in a 68% yield along with 13% ethyl isopropyl malonic ester. The mechanism by which the latter compound is formed is not obvious, but a similar malonic ester alkylation is known in which one of the chlorine atoms in carbon tetrachloride is replaced by hydrogen during reaction.[6]

An attempt to synthesize IXb by refluxing a suspension of dry sodium 2-nitropropane in a xylene solution of IVb was unsuccessful; only starting materials were recovered.

As a model of a 1-halo-nitroparaffin with an acidic hydrogen, 1-chloronitroethane, XII, was selected for reaction with sodium malonic ester. Under conditions similar to those described above for the reaction with Ia, the preponderant part of the ester was recovered, in spite of the fact that a great deal of solid material was precipitated during an exothermic reaction. Apparently the initial reaction is merely the regeneration of malonic ester from its sodium salt by the stronger acid XII. XII could not be regained, however, upon acidification of the salt material, which proved to be mainly sodium chloride rather than the expected sodium 1-chloronitroethane.

Experimental[7]

2-Bromo-2-nitropropane.[8]—The following procedure was used for the preparation of a pure starting material. 2-Nitropropane[9] (178 g., 2 moles) was dissolved, with external cooling, in a solution of 132 g. 85% potassium hydroxide pellets in 500 cc. of water. The resulting solution of sodium 2-nitropropane was cooled in an ice-bath while bromine (320 g., 2 moles) was dropped in with stirring at such a rate as to maintain the temperature at 35–40°. After the addition was complete, the reaction mixture was usually colored red; solid sodium sulfite was added with vigorous stirring until the mixture became colorless. The heavy, oily layer of the bromonitroparaffin was separated from the water layer and washed twice with 100-cc. portions of water. The product, after drying over sodium sulfate, was essentially pure, since 99% distilled at 151.7–151.8° (745 mm.) forerun: 150.5–151.7°); yield 89%. Many of the 1-halonitroparaffins are lachrymators, and care should be exercised in their use.

The Reaction of 2-Bromo-2-nitropropane with Sodium Malonic Ester.—Sodium malonic ester (0.4 mole) was prepared in 200 cc. of absolute alcohol contained in a 500-cc. three-neck flask equipped with a stirrer, thermometer, dropping funnel and reflux condenser with calcium chloride tube attached (a similar set-up was used in the subsequently described experiments). 2-Bromo-2-nitropropane (33.6 g., 0.2 mole) was dropped in with stirring over a period of twenty-five minutes; the temperature of the contents was maintained at 35° by external cooling. Stirring was continued at room temperature for four hours. Petroleum ether (50 cc.) was added and the flask cooled in an ice-bath and the contents filtered. The colorless material collected was washed with petroleum ether and was then added to 200 cc. of water. The salts dissolved, and the white needles of ethane tetracarboxylic ester which floated on top were filtered off and dried at 60°; yield, 41.6 g., m.p. 72–73°. After two recrystallizations from alcohol–petroleum ether, the melting point was 75.0–75.3°, which was not depressed upon admixture with an authentic sample (m.p. 75.0–75.3°).[10] Approximately five additional g. of the ester may be obtained from the initial alcoholic mother liquor by removing the excess alcohol and adding an excess of water; the thick oil which comes down is redistilled under reduced pressure.

The identity of the sodium 2-nitropropane which was obtained mixed with the ester was indicated in the following way. The aqueous solution obtained when the mixture was added to water was acidified with sodium bisulfite, the resulting 2-nitropropane extracted with ether and identified by its boiling point and conversion to the blue monomeric isopropylpseudonitrole, $(CH_3)_2C(NO)NO_2$, by means of nitrous acid (red, white and blue test).

Reaction of 2-Bromo-2-nitropropane with Sodium Ethyl Malonic Ester.—2-Bromo-2-nitropropane (50.4 g., 0.3 mole) was added dropwise over a period of four minutes to a solution of 0.32 mole sodium ethyl malonic ester in 175 cc. absolute alcohol maintained at 40° by external cooling. Stirring was continued for ten minutes. The thick mush of sodium 2-nitropropane and sodium bromide which had formed was filtered off with suction and washed

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[6] O. Dimroth, *Ber.*, **35**, 2883 (1902).

[7] All melting points corrected. All yields based upon the amount of starting material consumed.

[8] V. Meyer and J. Tscherniak, *Ann.*, **180**, 118 (1876).

[9] Eastman Kodak Co. practical grade was redistilled with a Todd column: b. p. range, 119.7–120.0° (745 mm.)

[10] H. F. Finkelstein, *Ber.*, **43**, 1532 (1910).

with 50 cc. of ether. The salt mixture was then triturated with 200 cc. of ether and again filtered. The ether washings were added to the main filtrate. The excess ether and alcohol was removed by distillation under reduced pressure using a heating mantle; the internal temperature was not allowed to rise above 95°. After cooling to room temperature, 100 cc. of water was added and the two phases were allowed to stand overnight. After this time, a small amount of snow-white crystals had separated from the ethyl bromomalonic ester layer. It was filtered off, washed with a few cc. of ether and dried at room temperature (1.5 g.). The melting point 215.0–215.5° was not lowered upon mixing with 2,3-dinitro-2,3-dimethylbutane[2] (m.p. 215.5–216.0°, purified by sublimation). The halomalonic ester was separated from the water layer and the latter extracted with 50 cc. of ether. The combined ester and extract were dried over sodium sulfate. Fractionation was begun in a Todd column but had to be discontinued after a forerun of 14.5 g. ethyl malonic ester had been collected, since the dinitrohexane which sublimed at the same time clogged the narrow takeoff passage. Distillation was continued from a Claisen flask. Two rectifications gave 44.0 g. of ethyl bromomalonic ester, b.p. 121–124° (12 mm.). The product was contaminated with small amounts of the dinitrohexane, which could not be completely removed by further fractionation. The infrared spectrum of a middle cut was identical with that of an authentic sample[11] (b.p. 124.0° (11.5 mm.) cor.) which had been saturated with dinitrohexane for comparison purposes.

Reaction of 2-Chloro-2-nitropropane with Sodium Malonic Ester.—2-Chloro-2-nitropropane (24.7 g., 0.2 mole), b.p. 88.5–88.7° (174 mm.), was added in one lot to 0.4 mole of sodium malonic ester dissolved in 200 cc. absolute alcohol. Stirring was continued for sixty-five hours while the internal temperature was maintained at 40–45° by a heating mantle. Stirring was discontinued, and the mixture of salts which had precipitated was filtered out. The excess alcohol was then removed under reduced pressure and 100 cc. of water added. The ester layer was separated and one ether extract of the water layer added to it. After drying over sodium sulfate, fractionation was begun in a Todd column. After a forerun of malonic ester, 17.6 g. (44%) of isopropylidene malonic ester was collected. The remainder was distilled from a Claisen flask, yielding 19.6 (27%) of isopropylidene dimalonic ester (b.p. 195–200° (12 mm.)). The unsaturated ester was identified by a characteristic, known reaction:[12] the concomitant ammonation and hydrolytic cleavage to acetone (isolated as the semicarbazone, m.p. 190.0–191.5°) and malonamide (m.p. 173.2–173.6°; mixed m.p. 173.2–173.6°). The reported melting points of these compounds are, respectively, 190–191° and 170°.[13] The tetra-ester was hydrolyzed to 2,2-dimethyl-1,5-pentanedioic acid (m.p. 99.8–100.0°); the anhydride (m.p. 125.0–125.5°) and the monoanilide (m.p. 135.0–135.5°) were prepared. The melting points given in the literature are, respectively, 100–101°[14] (103–104°[15]), 124°[14] and 131°.[16]

1-Nitro-1-methylethyl Ethyl Malonic Ester.—2-Chloro-2-nitropropane (123.5 g., one mole) was added dropwise over a period of four to five hours to a refluxing, stirred solution of one mole of sodium ethyl malonic ester in 550 cc. of dry ether. Refluxing and stirring were continued for thirty-six hours. The excess ether was removed by distillation under diminished pressure and the crude ester isolated in the manner previously described. Fractionation with a Todd column gave 47 g. unreacted 2-chloro-2-nitropropane and 18.5 g. ethyl isopropyl malonic ester (b.p 129.5–132.0° (20 mm.); 231–234° (742 mm.)). Crossley and Le Sueur[17] give 232–233° as the boiling point of the latter compound. The remaining, undistilled ester was transferred to a Claisen flask and 116 g. of 1-nitro-1-methylethyl ethyl malonic ester collected at 161–165° (14.0 mm.). A middle cut boiling at 164.0° (14.0 mm.) was used for analysis.

Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.42; H, 7.69; N, 5.09; mol. wt., 275; sapn. equiv., 91.8.[18] Found: C, 52.68, 52.56; H, 7.17, 7.06; N, 5.17; mol. wt. (Rast), 276; sapn. equiv., 89.8; $n^{22}\text{D}$ 1.4335. The Bose[19] method for the detection of a nitrite or nitro group was positive. The infrared spectrum of the ester showed distinct absorption maxima at 1550 and 1350 cm.$^{-1}$; the characteristic maxima of the nitro group are at 1550 and 1380 cm.$^{-1}$ whereas those of the nitrite group fall at 1660–1730 and 1160 cm.$^{-1}$.[20]

The infrared spectrum of the ethyl isopropylmalonic ester was not identical with that of an authentic sample; however, they were so nearly so that the slight discrepancy may be assumed to be due to an impurity in the experimental product.

Acknowledgment.—The authors wish to express their gratitude to the Commercial Solvents Corporation, who supplied the chloronitroparaffins used in this investigation.

Summary

2-Bromo-2-nitropropane reacts with sodium malonic esters to give, as the initial products, sodium 2-nitropropane and bromomalonic esters. Additional products encountered are described. A "positive bromine ion" mechanism is proposed.

2-Chloro-2-nitropropane reacts normally with sodium malonic esters to give 1-nitro-1-methylethyl malonic esters as the initial products. In the case of the reaction with unsubstituted malonic ester, the nitroalkyl malonic ester is unstable and loses the elements of nitrous acid to yield isopropylidene malonic ester.

HOLLAND, MICHIGAN RECEIVED SEPTEMBER 27, 1948

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(13) J. V. Backes, R. W. West and M. A. Whitely, *J. Chem. Soc.*, **119**, 359 (1921).

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(16) W. H. Perkin, Jr., *J. Chem. Soc.*, **69**, 1476 (1896).

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(18) Assuming the complete displacement of the nitro group, which apparently takes place under the drastic conditions necessary for complete saponification, *viz.*, refluxing for two hours in an ethylene glycol solution of potassium hydroxide.

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