[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Tricyclic Hydrocarbons Related to Stilbestrol

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In the search for an explanation of the unusual physiological activity of diethylstilbestrol (I), Dodds, *et al.*,[1,3] and Campbell, *et al.*,[2] have pointed out that there is a definite structural resemblance of this compound to estrone. The two compounds differ only by two hydrogens and their molecular sizes are probably quite similar. Dihydro-diethylstilbestrol possesses approximately the same activity as estrone and, incidentally, answers to the same formula, $C_{18}H_{22}O_2$.

The theory demands that both of these synthetic estrogens should exist in two isomeric forms. In the case of diethylstilbestrol, the two isomeric forms are *cis* (II) and *trans* (I), and dihydrodiethylstilbestrol derives its isomers from the possession of two asymmetric carbon atoms. All four of these compounds have been isolated and their activity tested.[1,2,4] In both cases the higher-melting isomer was found to be the more active. The belief that the higher-melting diethylstilbestrol is the *trans* form, is probably justified (based on the comparison of physical constants), and it agrees with the theory of similarity to estrone outlined above. Any conclusions as to the structure of the saturated compound must be on a purely physiological basis, since the physical constants do not permit any differentiation of the meso and racemic forms. There is, however, insufficient evidence available that the similarity to estrone is the decisive factor.

This similarity would be even more pronounced if cyclization of these compounds were effected to structures such as (IV), (V), (VI), and the dihydroxy derivative of (VII). That a ring closure such as this is unlikely to occur in the animal organism, does not necessarily exclude the possibility that the final chrysene or indene derivatives might be equally active or stronger estrogens than the parent compound. A similar idea was expressed by Campbell,[5] who suggested a connecting link between the most potent members which concerns "the apparent possibility of ring closure of certain estrogens to give compounds containing cyclopentane rings with incidental methyl groups." The *trans* form of (IV) has been tested for its estrogenic activity and found to be very much weaker than diethylstilbestrol, and of about the same order of magnitude as (IIIb); whereas (V), prepared by Dodds, *et al.*,[1] was only about one-tenth as active.

Comparing the estrogenic activity of compounds possessing the characteristic group PhC–CPh, the following general conclusions may be drawn: (a) saturation of the ethylenic linkage reduces the activity, and (b) the compound must be in a definite, as yet unknown, stereochemical configuration, in order to show maximum activity.

The effect of cyclization to saturated and unsaturated five-membered rings, cyclization to unsaturated six-membered rings, as well as the study of stereochemical isomers in the saturated series, still remain to be investigated.

Since the knowledge of the effect of such cyclizations would throw some light upon the relation of physiological activity to chemical constitution, it seemed desirable to investigate compounds of this type. With the exception of (IV) and (V), neither these polycyclic phenols nor their corresponding hydrocarbons are known, and this research is therefore concerned with the investigation of methods whereby such compounds can be prepared.

By means of the method developed in this research, a path has been opened to the synthesis of indane, as well as dihydronaphthalene, derivatives of structures (VI) and (VII). The hydrocarbons (VII) and (XXII) have been prepared as outlined in Flow Sheet B. The starting material for both compounds was ethyl phenylcyanacetate (XIII), conveniently prepared according to the procedure reported for the corresponding *p*-methoxy compound by Niederl, Roth and Plentl.[6] This ester was condensed with α-phenylethyl bromide, to give the disubstituted cyanoacetic ester (XIV) and, as by-product, one

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(1) Dodds, Golberg, Lawson and Robinson, *Proc. Roy. Soc.* (London), **B127**, 140 (1939).

(2) Campbell, Dodds and Lawson, *ibid.*, **B126**, 253 (1940).

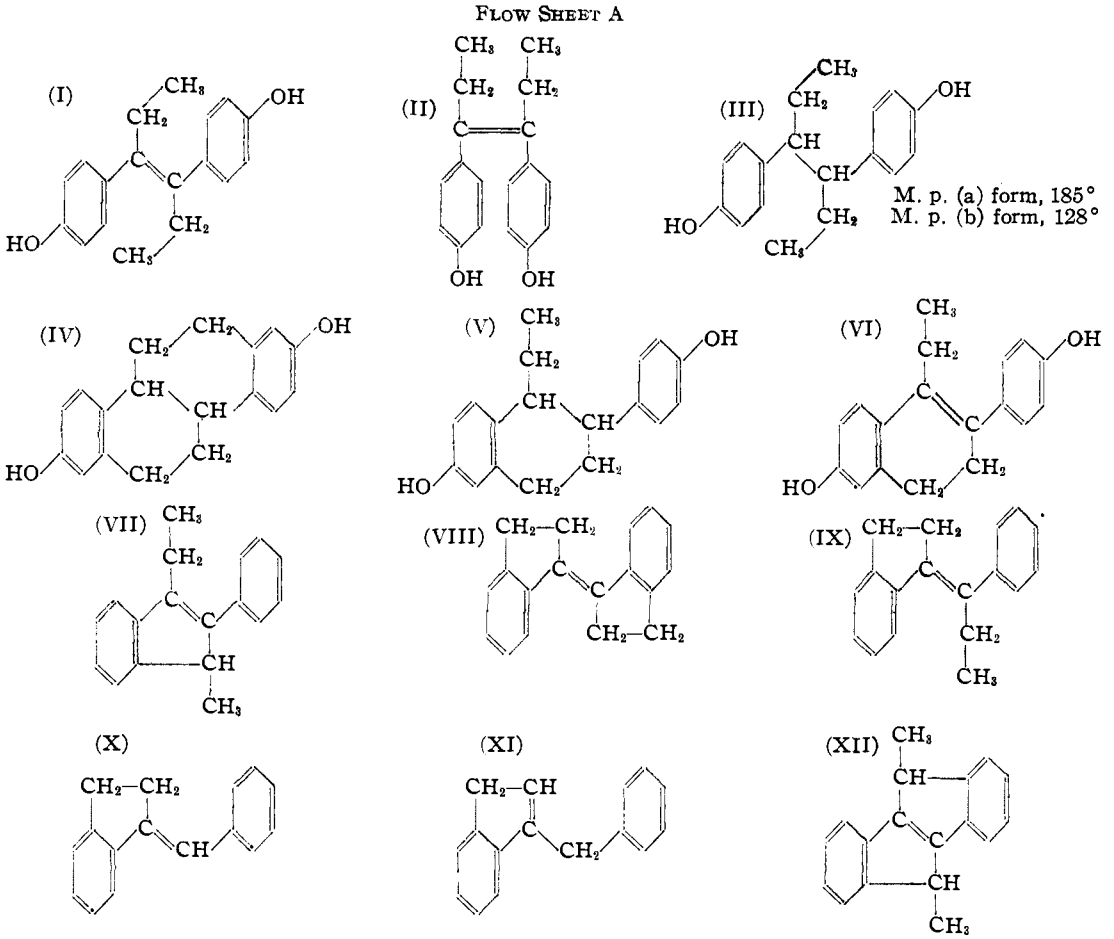
(3) Cook, Dodds, Hewett and Lawson, *ibid.*, **B114**, 286 (1934).

(4) Docken and Spielman, THIS JOURNAL, **62**, 2163 (1940). See also British Patent Specification No. 523,320, of Boots Pure Drug Co., Ltd., and W. F. Short, of Dec. 30, 1938; *Chem. and Ind.*, **59**, 703 (1940).

(5) Campbell, *ibid.*, **58**, 1087 (1939).

(6) Niederl, Roth and Plentl, THIS JOURNAL, **59**, 1901 (1937).

FLOW SHEET A



of the two isomeric α,β-diphenylbutyronitriles (XV).[7]

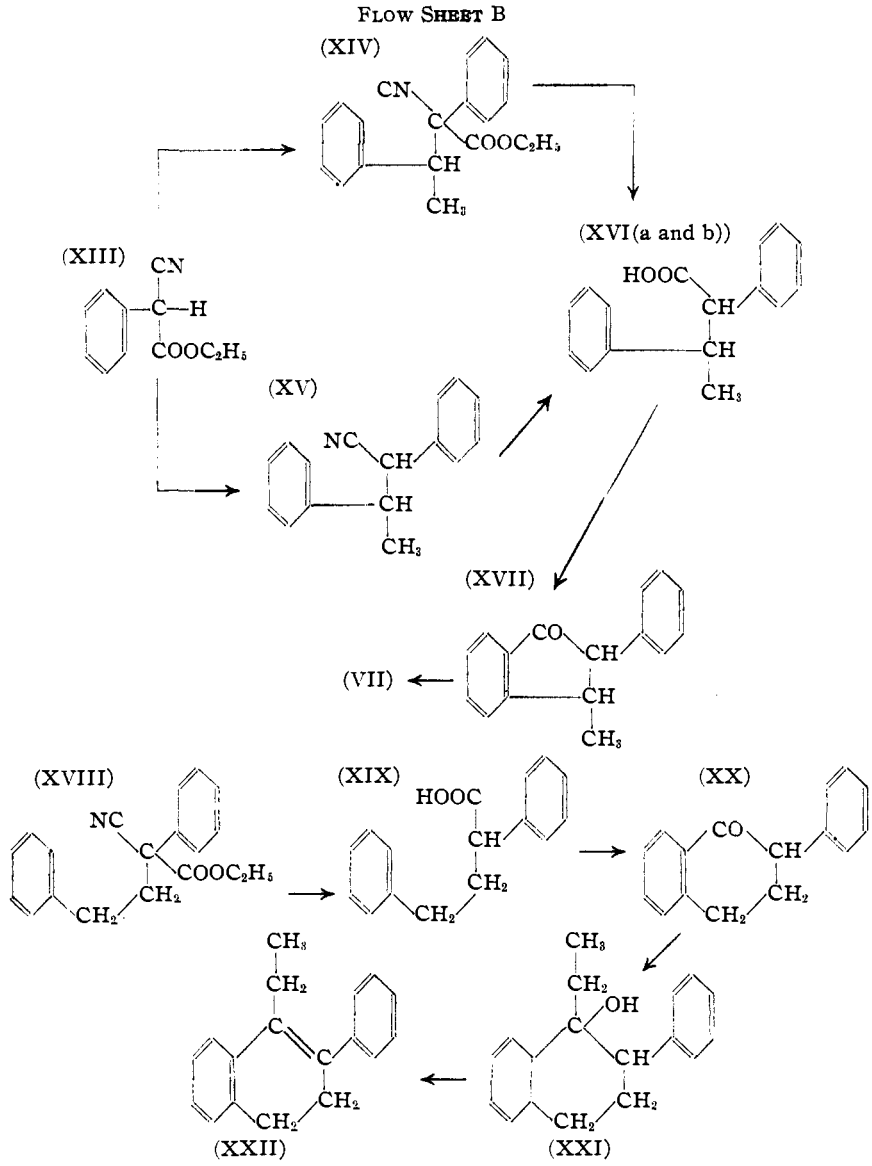
Cope and McElvain[8] studied the decomposition of disubstituted malonic esters under the influence of sodium ethylate, and found that the decomposition proceeds with formation of the ethyl ester of the monobasic acid and diethyl carbonate, the nature of the substituent groups determining the readiness with which the cleavage takes place. An analogous decomposition was found to occur in this case at the temperature of boiling alcohol.

Saponification and decarboxylation of the cyanacetic ester (XIV) was carried out in a bomb tube, using a mixture of acetic and hydrochloric acids. Saponification in alkaline solution was also studied under various conditions, but was abandoned in favor of the acid hydrolysis. The acid resulting from this reaction (XVI) was obtained as a mixture of diastereoisomers, the separation of which yielded two pure racemic modifications, one melting at 136° and the other at 186°. Ramart-Lucas,[7] who prepared these acids by saponification of the two isomeric α,β-diphenylbutyronitriles (XV), reported their melting points as 133–134° and 181°.

The cyclization was effected by means of a Friedel–Crafts reaction, using carbon disulfide as solvent; no other solvent usually employed for these reactions was found to be satisfactory, due to the insolubility of the acid chloride. The indanone (XVII), a rather unstable compound, exhibited carbonyl characteristics, as indicated by the formation of a 2,4-dinitrophenylhydrazone, but failed to form a semicarbazone under the usual conditions. This was probably due to the influence of the phenyl group at C_2, causing enolization in the presence of the alcoholic sodium acetate buffer. The ketone reacted with ethylmagnesium iodide with formation of the unsaturated hydrocarbon, after dehydration of the intermediate tertiary alcohol by acetic anhydride.

(7) Ramart-Lucas, *Ann. chim.*, [8] **30**, 424 (1913).
(8) Cope and McElvain, THIS JOURNAL, **54**, 4319 (1932).

FLOW SHEET B



The condensation of the cyanacetic ester (XIII) with β-phenylethyl bromide was much more difficult than in the case of its α-isomer. Using dioxane as solvent, according to the modification of Finkelstein and Elderfield,[8] the reaction went to completion within about forty hours; while in ethyl alcoholic solution, refluxing for more than one hundred hours gave contaminated products in poor yield. Decomposition of this ester did not seem to take place to any appreciable extent, although the analytical figures are somewhat off.

The resulting cyanobutyric ester (XVIII) was saponified in the same manner as (XIV) to the α,γ-diphenylbutyric acid (XIX). Cyclization of this acid proceeded smoothly, and without formation of by-products, in 85–90% yield. The comparative ease of cyclization of α,β- and α,γ-diphenylbutyric acids to the tetralone and indanone derivatives, is quite in agreement with the observations of Braun,[9] Braun, Bayer and Cassel,[10] and Leuchs,[11] that formation of hydroaromatic six-membered rings on benzene rings proceeds more easily than that of five or seven-membered rings.

The tetralone (XX) like the indanone (XVII) did not react with semicarbazide hydrochloride, but formed a dinitrophenylhydrazone. When treated with ethylmagnesium iodide, it formed a tertiary alcohol (XXI), which was isolated in this case. Dehydration to 2-phenyl-1-ethyl-3,4-dihydronaphthalene was effected by boiling the tertiary alcohol with concentrated hydrochloric acid.

Since Niederl, Roth and Plentl[6] have shown that ethyl *p*-methoxyphenylmalonate can be used for alkylation of anisole derivatives, the above synthesis should be repeatable using as starting material the *p*-methoxyphenylmalonic ester and α- or β-anisyl ethyl bromide. The desired methoxy compounds or phenols, of (VI) and (VII) type, should be thus obtainable.

In attempting to synthesize a hydrocarbon analogous to the third possible cyclization product of diethylstilbestrol (VIII), difficulties were encountered.

Since a direct route to the essential Ph—C≡C—

(9) Braun, *Ber.*, **61**, 441 (1928).
(10) Braun, Bayer and Cassel, *ibid.*, **60**, 2602 (1927).
(11) Leuchs, *ibid.*, **61**, 144 (1928).

Ph arrangement is the dehydration of an α- or β-tertiary alcohol, and since these alcohols are most conveniently prepared by a Grignard reaction, the carbonyl characteristics of indanone with respect to these reagents were studied and an attempt made to prepare a Grignard reagent of indanyl chloride. The latter was entirely unsuccessful, but indanone was found to react normally with alkylmagnesium halides.

The reaction of benzylmagnesium chloride produced a tertiary alcohol which, after dehydration during an attempted distillation, gave (X) in good yield. The location of the double bond in this compound was shown by oxidative degradation. Oxidation with cold alkaline permanganate gave benzoic acid; and oxidation with permanganate in acetone solution produced indanone, identified as its semicarbazone. In view of the fact that these oxidation products were obtained in poor yield, it is quite possible that the product might have contained some of the isomer (XI).

Attempts to prepare the indanone derivative (IX) were unsuccessful, since the Grignard reagent of α-phenylpropyl bromide could not be prevented from reacting with the free bromide present in the mixture. This latter reaction seemed to enjoy preference over that with the carbonyl, since the condensation product, γ,δ-diphenylhexane, was formed even when the Grignard reagent was prepared in the presence of indanone.[12] Docken and Spielman[4] in a recent paper successfully used this method for the preparation of the higher-melting form of dihydrodiethylstilbestrol.

Acknowledgments.—This research could not have been carried out but for the generous assistance of E. R. Squibb & Sons, to whom we are most grateful. We are also indebted to Mr. Saul Gottlieb, by whom the analyses were conducted.

Experimental

1-Benzalindane (X).—To a Grignard reagent prepared from 2.4 g. of magnesium, 12.6 g. of benzyl chloride, and 200 cc. of anhydrous ether, there was added a solution of 13.2 g. of freshly distilled 1-indanone in 50 cc. of anhydrous ether. The addition was carried out as slowly as possible, with rapid stirring and cooling in ice. When all of the indanone had been added, stirring and cooling were continued for three hours and the mixture was then refluxed for twenty minutes on the steam-bath. The reaction mixture was poured upon ice and decomposed with ammonium chloride and a small amount of hydrochloric acid. The ether layer turned bright yellow, while the water layer remained colorless. The former was drawn off, dried with magnesium sulfate overnight, filtered, the solvent removed under reduced pressure at room temperature, and the residue transferred to a small distilling flask. After a troublesome elimination of water and repeated distillation, the product boiled at 157–157.5° (2 mm.); yield, 65%.

Since the distillate remained yellow even after several distillations, an attempt was made to purify the compound further by chromatographic adsorption. A 5% solution in Skelly Solvent B was allowed to flow through a 20 cm. column of aluminum oxide. All the material was adsorbed and eluated with a Skelly Solvent–benzene mixture and finally washed through the column with pure benzene. Only a small brown ring remained in the upper part of the chromatogram.

After elimination of the benzene, the residue was once more distilled. Its boiling point had not changed: b. p. 157–157.5° at 2 mm., d^{25}_4 1.0571, $n^{25}D$ 1.6100, R_L calcd. 67.4, found 67.6.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.3; H, 6.7. Found: C, 93.4; H, 7.0.

Oxidation of (X) in Alkaline Solution.—2.01 grams of the hydrocarbon (X), 2.5 g. of anhydrous potassium carbonate, and a little water were placed in a one-liter flask provided with an efficient stirrer and dropping funnel. The stirrer was set in motion, the flask cooled in ice and 150 cc. of a 3% permanganate solution added drop by drop, over a period of three hours. The mixture was left for twelve hours, the slight excess of permanganate destroyed with a little oxalic acid, and the solution filtered. The manganese mud was washed four times with boiling water, the combined filtrates acidified, extracted with ether, and worked up as usual. The residue after the evaporation of the ether crystallized slowly and was dark brown. It was transferred to a sublimation apparatus and sublimed at 1.5 mm. The 220 mg. of sublimate, crystallized from dilute alcohol, had a melting point of 122° which showed no depression when mixed with an authentic sample of benzoic acid.

Oxidation of (X) in Neutral Solution.—500 mg. of the hydrocarbon was dissolved in 50 cc. of acetone, purified by repeated distillation over potassium permanganate, and a saturated solution of potassium permanganate in acetone was added until an additional drop produced a permanent color. The mixture was then refluxed for a short time and a few more drops of the permanganate solution added. The solution was left for four hours, decolorized with a little sulfurous acid and filtered. After removal of the solvent, the residue was dissolved in alcohol and the ketonic portion converted into its semicarbazone by the usual procedure; yield 100 mg. When recrystallized from dilute alcohol, the semicarbazone had a melting point of 239–240° and gave no depression with an authentic sample of 1-indanone semicarbazone.

α,β-Diphenylbutyronitrile (XV).—2.3 grams of clean sodium cuttings was added to 75 cc. of absolute ethyl alcohol. When all the sodium had dissolved, 18.9 g. of ethyl phenylcyanoacetate was added, the mixture refluxed for ten minutes, and then allowed to cool to room temperature;

(12) Houben–Weyl, "Die Methoden der organischen Chemie," 2d. ed., Vol. 4, 1924, p. 810.

18.5 grams of α-phenylethyl bromide was added all at once and the mixture quickly heated to boiling. Sodium bromide soon began to precipitate and the solution became neutral to litmus within less than thirty minutes. A fairly large amount of diethyl carbonate was given off which was lost during the following heating on the steam-bath. The mixture was poured into a beaker, diluted with its own volume of water, and heated on the steam-bath until free of alcohol. The product was extracted with ether, the combined ether layers washed with water and separated, taking care that no water remained in the ether. The combined ether layers were allowed to stand in the icebox overnight.

The large cubical crystals which formed were removed and recrystallized from absolute alcohol. The ethereal filtrate was concentrated to about one-half its original volume and diluted with absolute alcohol. On standing in the icebox for several hours, another crop of crystals formed, but further standing in the icebox did not produce any more crystalline products. Both crops were combined and recrystallized from dilute alcohol; m. p. 133°; yield, 2.4 g. of pure product; previously reported m. p. 129–130°.[9,10]

Anal. Calcd. for $C_{16}H_{16}N$: C, 86.8; H, 6.8. Found: C, 86.8; H, 6.8.

Ethyl α-Cyano-α,β-diphenylbutyrate (XIV).—Evaporation of the above mentioned ether solution gave an oil, which was distilled under reduced pressure. The product was an extremely viscous oil, with a faint blue fluorescence; b. p. 157° at 0.2 mm.; yield, 18.2 g. of pure product; $n^{25}D$ 1.5483; d^{26}_4 1.0943; R_L calcd. 84.9, found 85.5.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 77.8; H, 6.5. Found: C, 78.0; H, 6.7.

Isomeric α,β-Diphenylbutyric Acids (XVI a and b).—The saponification of (XIV) and (XV) was carried out by the general procedure outlined below for α,β-diphenylbutyronitrile.

1.50 grams of the α,β-diphenylbutyronitrile, m. p. 133°, was sealed in a bomb tube with 25 cc. of hydrochloric–acetic acid mixture, in a ratio of 1:2, and heated for fourteen hours at 200°. The product crystallized in the tube in long needles, which were removed and recrystallized from dilute methyl alcohol. These crystals proved to be a mixture of the two acids reported by Ramart-Lucas.[7] They were separated by fractional crystallization. The less soluble acid was found to have a constant melting point of 186°; previously reported m. p. 181°.[7]

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.2; H, 6.9.

Amide.—200 mg. of α,β-diphenylbutyric acid, m. p. 186°, was converted into the acid chloride by means of an excess of thionyl chloride. The resulting solution was poured into concentrated ammonium hydroxide, the precipitated amide filtered out and recrystallized from dilute ethyl alcohol; m. p. 193°.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.2; H, 7.1. Found: C, 80.5; H, 7.2.

The more soluble acid was found to have a constant melting point of 135°, after many recrystallizations from alcohol and Skelly Solvent B; previously reported m. p. 133–134°.[7]

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.2; H, 7.0.

Amide.—This derivative was prepared as described above for the isomeric acid; recrystallized from dilute alcohol, m. p. 173–174°.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.2; H, 7.1. Found: C, 80.3; H, 7.2.

3-Methyl-2-phenyl-indanone-1 (XVII).—3.64 grams of the diphenylbutyric acid was placed in a 500 cc. flask and 7 g. of water-white thionyl chloride added. As soon as the reaction had died down, the mixture was refluxed on the steam-bath for fifteen minutes. After cooling to room temperature, the excess of thionyl chloride was removed under reduced pressure and the residue crystallized from petroleum ether until colorless and free of sulfur dioxide. The product was allowed to stand *in vacuo* over paraffin for twenty-four hours; yield, 1.92 g. of solid acid chloride.

1.90 grams of the recrystallized acid chloride was dissolved in 50 cc. of dry carbon disulfide and slowly added to a cooled suspension of 3 g. of white aluminum chloride in 50 cc. of dry carbon disulfide. Little or no reaction took place during the addition of the acid chloride, but when heated on the steam-bath the reaction was completed within fifteen minutes. After cooling, the complex was decomposed in the customary way, using 200 cc. of shaved ice and about 10 cc. of concentrated hydrochloric acid. The carbon disulfide layer was drawn off and the aqueous layer extracted with ether. The combined extracts were washed with sodium bicarbonate solution and water until neutral, and then dried with anhydrous magnesium sulfate. After filtration and removal of the solvents, the residue was crystallized from petroleum ether and petroleum ether–benzene mixtures, and finally from ethyl alcohol; giving a product of m. p. 86°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.4; H, 6.3. Found: C, 86.2; H, 6.5.

2,4-Dinitrophenylhydrazone.—This derivative was prepared according to the procedure of Shriner and Fuson.[13] It was recrystallized from chloroform and ethyl acetate, and mixtures of these solvents, and then had a m. p. of 204°. It gave a depression of about 20° in melting point when mixed with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{22}H_{18}N_4O_4$: C, 65.6; H, 4.5. Found: C, 65.6; H, 4.7.

3-Methyl-2-phenyl-1-ethyl-indene-1 (VII).—To a Grignard reagent prepared from 382 mg. of magnesium turnings, 10 cc. of absolute ether and 2.48 g. of ethyl iodide. there was added 3.54 g. of 3-methyl-2-phenyl-indanone-1, dissolved in 15 cc. of absolute ether. When all the indanone had been added, the mixture was refluxed for about one-half hour and then decomposed in the usual way with 100 cc. of 10% hydrochloric acid. The ether solution turned bright yellow under the influence of the acid, but the coloration disappeared when the solution was washed to neutrality. The extracts were dried with magnesium sulfate and, after removal of the solvent, a colorless oil remained which could not be brought to crystallization.

(13) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 148.

Without further purification, this oil—presumably the tertiary alcohol—was dissolved in 20 cc. of freshly distilled acetic anhydride and the solution heated on the steam-bath for twelve hours. The mixture was then poured into water and, when all the acetic anhydride was hydrolyzed, the product was extracted with benzene, dried, the solvent removed and the residue distilled under reduced pressure; 920 mg. of a bright orange viscous oil was obtained.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.3; H, 7.7. Found: C, 92.0; H, 7.5.

Ethyl α-Cyano-α,γ-diphenylbutyrate (XVIII).—4.6 grams of sodium was added to 400 cc. of pure dioxane which previously had been dried and distilled over sodium. The dioxane was heated to its boiling point under a reflux and the sodium powdered with an efficient stirrer. After cooling to room temperature, 37.5 g. of ethyl phenylcyanacetate (XIII) was added and the mixture heated for twelve hours at its boiling point. The sodium derivative of the cyanoacetic ester crystallized slightly below the boiling point of the dioxane. When all the sodium had reacted, 39 g. of β-phenylethylbromide was added and the stirring and refluxing continued for forty hours, by which time the solution had become practically neutral. It was centrifuged, the salt washed twice with dioxane, and the combined dioxane washings and original solution concentrated under reduced pressure until almost all the solvent was removed. The residue was then taken up in ether and washed with water. The ether extracts were dried with magnesium sulfate and the product worked up in the usual manner, giving 18 g. of pure product, b. p. 174–175° at 0.5 mm., $n^{25}D$ 1.5453, d^{25}_4 1.0882, R_L calcd. 85.5, found 85.0.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.8; H, 6.5. Found: C, 78.3; H, 6.5.

α,γ-Diphenylbutyric Acid (XIX).—Ten grams of the cyanobutyric ester was saponified and decarboxylated, by heating in a bomb tube with 20 cc. of acetic and 30 cc. of concentrated hydrochloric acid at 200° for fourteen hours. The product consisted of a liquid, containing some crystalline material. The contents of the bomb tube was poured into an Erlenmeyer flask containing 200 cc. of water and, after standing for three days, almost all of the material had crystallized. The crystals were filtered out, the remaining water removed by desiccation *in vacuo* overnight, and the product pressed out on a porous tile. Recrystallized from Skelly Solvent B, the yield was almost that calculated, and the m. p. 76°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.0; H, 6.9.

2-Phenyltetralone-1 (XX).—1.4 grams of pure α,γ-diphenylbutyric acid was mixed with 4 cc. of pure thionyl chloride and refluxed on the steam-bath until no more hydrochloric acid was given off. The excess of thionyl chloride was removed under reduced pressure and the residual liquid chloride dissolved in 20 cc. of carbon disulfide. This solution was slowly added to a suspension of 2.5 g. of aluminum chloride in 50 cc. of carbon disulfide. Evolution of hydrochloric acid gas soon began to set in and the mixture was refluxed for one-half hour. After cooling to room temperature, the mixture was poured upon ice containing 5 cc. of concentrated hydrochloric acid and then allowed to stand in the icebox overnight. The carbon disulfide layer was removed, the aqueous layer extracted with chloroform, and the combined extracts washed with sodium bicarbonate solution and water until free from acid. After drying with magnesium sulfate and evaporation of the solvent at room temperature, the residue was crystallized from petroleum ether and then had a m. p. of 79°; yield, 1.02 g. of pure product.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.4; H, 6.3. Found: C, 86.6; H, 6.6.

2,4-Dinitrophenylhydrazone.—This derivative was prepared according to the procedure of Shriner and Fuson[13] using 200 mg. of the ketone and 150 mg. of 2,4-dinitrophenylhydrazine. The product formed slowly in the hot and was recrystallized from ethyl acetate, when its m. p. was 198°. It was much darker orange than its isomer (m. p. 204°) and gave a depression of over 25° when mixed with the free base.

Anal. Calcd. for $C_{22}H_{18}N_4O_4$: C, 65.6; H, 4.5. Found: C, 65.3; H, 4.5.

1-Ethyl-2-phenyl-1,2,3,4-tetrahydronaphthol-1 (XXI).—3.54 grams of 2-phenyltetralone, dissolved in 15 cc. of absolute ether, was added to a cooled Grignard reagent prepared from 382 mg. of magnesium and 2.48 g. of ethyl iodide in 20 cc. of absolute ether. The mixture was stirred for one-half hour and then refluxed for about one hour, cooled to room temperature, and worked up in the usual manner using dilute hydrochloric acid to decompose the product. The ether layers were washed to neutrality and, after drying with magnesium sulfate, the solvent was removed under reduced pressure. The residue crystallized slowly in the icebox and was freed from adherent oil by pressing on a porous tile. The crystalline material was recrystallized from low-boiling petroleum ether. After concentration of all mother-liquors, 1.10 g. of pure tertiary alcohol, m. p. 129°, was obtained.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.7; H, 7.9. Found: C, 85.6; H, 8.0.

1-Ethyl-2-phenyl-3,4-dihydronaphthalene (XXII).—700 mg. of the tertiary alcohol was refluxed with 40 cc. of concentrated hydrochloric acid for one hour. The mixture was allowed to cool to room temperature and the acid neutralized with dilute sodium hydroxide. The neutral solution was subjected to steam distillation and one liter of distillate collected. This distillate was extracted with benzene, the benzene extracts washed and dried. After concentration of these extracts to about 10 cc., the solution was transferred to a small molecular still, the concentration continued and the product distilled at 0.1 mm., bath temperature 80–90°. 200 mg. of a colorless viscous oil was collected.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.3; H, 7.7. Found: C, 92.3; H, 7.6.

Summary

1. 1-Ethyl-2-phenyl-3,4-dihydronaphthalene, 3-methyl-1-ethyl-2-phenylindene and a number of intermediate compounds were synthesized by a method which establishes their structure.

2. The method developed in the preparation of these hydrocarbons is of such a nature that it should be applicable to the preparation of those corresponding methoxy and phenolic compounds believed likely to possess estrogenic activity, and experimental work in this direction is already under way.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Action of Halogens on α,β-Unsaturated Ureides

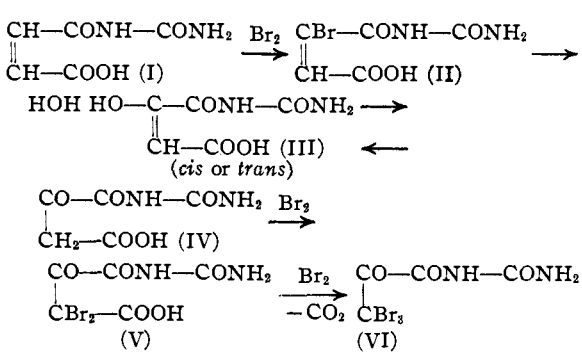
BY CHESTER J. CAVALLITO AND CLAYTON S. SMITH

Unsaturated ureides of the type R—CH=CH—CONH—$CONH_2$ might be expected to react with halogens to form addition products of the type RCHX—CHX—CONH—$CONH_2$. However while attempting to prepare dibromosuccinuric acid, HOOC—CHBr—CHBr—CONH—CONH—$CONH_2$ by treating maleuric acid, $\begin{matrix}CH—CONHCONH_2\\ \|\\ CH—COOH\end{matrix}$, with bromine water, instead of the expected dibromo addition product, a white crystalline solid was obtained. This compound dissolved readily in alkalies and yielded almost immediately a white cloudy precipitate identified as bromoform. The production of bromoform by treatment of the bromination product of maleuric acid with alkali was an indication of the presence of a CBr_3—CO— instead of a —CHBr—CHBr— group in the molecule. A study was then conducted to determine the nature of the reaction of halogens, particularly bromine with maleuric acid, as well as the behavior of other unsaturated ureides with halogens.

Reaction of Bromine Water with Maleuric Acid.—The product obtained at room temperature was analyzed for C, H, N, and Br, and the empirical formula $C_4H_3O_3N_2Br_3$ obtained. The bromoform was obtained in practically quantitative yield by treatment with alkali. At about 5° the brominated product could be titrated as a monobasic acid. A mono-silver salt could also be obtained. This acidic character was attributed to a —CO—NH—CO— rather than to a carboxyl group since attempts to esterify the compound were unsuccessful. Alkaline hydrolysis of the tribromo derivative also yielded oxalic acid quantitatively, and some urea. Milder alkaline hydrolysis produced oxaluric acid, which could be easily broken down into oxalic acid and urea. This established the presence of a —CO—CO—NH—CO—NH_2 group in the molecule as well as CBr_3—CO—; thus, the compound was shown to be CBr_3—CO—CONH—$CONH_2$, tribromopyruvyl urea, previously prepared by Emil Fischer.[1]

The synthesis of tribromopyruvyl urea from maleuric acid must have involved several intermediate steps. In an effort to isolate the intermediates, maleuric acid was treated with bromine water at 0–10°. A yellow compound was obtained which from analysis appeared to be a monobromo substitution product of maleuric acid. The same monobromide was obtained by treating maleuric acid with bromine in carbon tetrachloride.

The monobromide did not liberate iodine from a potassium iodide solution, indicating that bromine was not attached to nitrogen. Heating with water to about 60–70° caused decomposition with the formation of carbon dioxide, Br^-, and some ammonia. If the monobromide were dissolved in cold alkali, and the solution acidified, a white compound was obtained which no longer contained bromine, but was not maleuric acid. Treatment of either the monobromide or its debromination product with bromine water at room temperature led to the formation of tribromopyruvyl urea. The analytical results and the chemical properties of the intermediate compounds indicated that the reaction of bromine water with maleuric acid proceeded as follows



(1) Emil Fischer, *Ann.*, **239**, 185 (1887).