354. *Experiments on the Synthesis of Substances related to the Sterols. Part XXVIII.*

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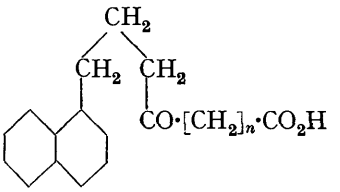
The tetracyclic ketones (III, R = H and R = OMe) have been synthesised by the keto-acid method of Robinson and Schlittler. The two ring-closures of this process can be brought about in one operation in certain cases.

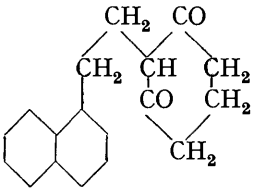
THE condensation of γ-1-naphthylbutyryl chlorides with ethyl sodioacetylsuccinate and ethyl sodio-α-acetylglutarate so as to obtain eventually desirable tetracyclic ketones was undertaken in this laboratory as a natural extension of the long-chain keto-acid method of Part III (Robinson and Schlittler, J., 1935, 1288).

In the meantime, the synthesis of *x*-norequilenin (Part XXII, Koebner and Robinson, J., 1938, 1994) from much more readily available intermediates has rendered the use of the above synthetic method unnecessary for some purposes. In view of this and because of the appearance of a series of papers by Chuang and his co-workers (Chuang, Tien, and Huang, *Ber.*, 1937, **70**, 858; Chuang, Huang, and Ma, *Ber.*, 1939, **72**, 713; Chuang, Ma, Tien, and Huang, *ibid.*, p. 949) dealing with the same obvious development of the method of Part III, we now submit our results, even though the final stages have not yet been accomplished.

γ-1-Naphthylbutyric acid and its α-methyl derivative were used to test the possibilities in this field before the less accessible 6-methoxy-compounds were employed. The condensation of γ-1-naphthylbutyryl chloride with ethyl sodioacetylsuccinate and ethyl sodio-α-acetyglutarate gave good yields of *4-keto-7-α-naphthylheptoic acid* (I, $n = 2$) and 5-keto-8-α-naphthyloctoic acid (I; $n = 3$) respectively, but the introduction of an α-methyl group led only to the regeneration of all the naphthylbutyric acid used when the condensation product from γ-1-naphthyl-α-methylbutyryl chilorde and ethyl sodioacetylsuccinate or ethyl sodio-α-acetylglutarate was hydrolysed. Chuang, Ma, Tien, and Huang (*loc. cit.*), using γ-(6-methoxy-1-naphthyl)-α-methylbutyryl chloride, record a similar failure and in Part XVIII (Peak and Robinson, J., 1937, 1581) it was noted that nordihydrocitronellic acid, also containing an α-methyl group, failed to yield any keto-acid on condensation of its chloride with ethyl sodioacetylsuccinate and hydrolysis of the product.

(I.)



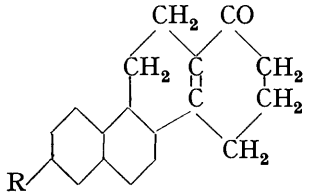


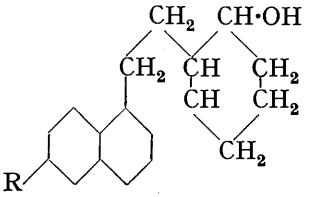
(II.)

Cyclisation of the methyl ester of (I, $n = 3$) gave β-1-*naphthylethyl*cyclo*hexane*-2 : 6-*dione* (II), which was dehydrated by means of phosphoric anhydride in damp benzene to 3-*keto*-1 : 2 : 3 : 4 : 5 : 6-*hexahydrochrysene* (III, R = H), characterised as its 2 : 4-*dinitrophenylhydrazone*. Of the cyclodehydrating agents, 90% phosphoric acid at 100°, boiling acetic anhydride, and phosphoric anhydride in boiling benzene, the last gave much the best results, but the efficiency of the process was very dependent on the degree of dampness of the benzene. In preliminary experiments the action of sodium ethoxide on the methyl ester of (I, $n = 2$) gave no pseudo-acidic product and dilute mineral acid precipitated syrupy material which could not be crystallised. This was taken as an indication of failure to obtain the *cyclo*pentane-2 : 5-dione. Nevertheless the cyclodehydration of this crude material gave 3'-keto-3 : 4-dihydro-1 : 2-*cyclo*pentenophenanthrene and it appears that a double ring-closure of the keto-acids may be brought about in this case. This view is supported by the fact that the double ring-closure of methyl ketonaphthyloctoate to (III, R = H) was also realised. For these reasons we doubt the validity of the claim of Chuang to have prepared a *cyclo*pentanedione by ring-closure of a keto-ester.

The successful preparation of the ketone (III, R = H) led us to synthesise 3-keto-10-methoxy-1 : 2 : 3 : 4 : 5 : 6-hexahydrochrysene (III, R = O·CH_3) by the same route from

(III.)





(IV.)

γ-(6-methoxy-1-naphthyl)butyric acid. The yield in the final ring-closure was much better in this case, and constitutes a great improvement upon that recorded by Chuang, Tien, and Huang (*loc. cit.*).

To synthesise *x*-norequilenin from (III, R = O·CH_3), the ethylenic linkage would be saturated and the *cyclo*hexanone ring degraded to a *cyclo*pentanone ring. Only the first stage was studied; this appeared to be difficult and must probably be carried out through the stage of a saturated secondary alcohol which could subsequently be reoxidised to the saturated ketone by the reversed Pondorff method of Oppenauer. A p-*nitrobenzoate* of (IV, R = O·CH_3 or O·C_2H_5) was obtained. Analysis indicated that methoxyl was probably replaced by ethoxyl in the course of the reaction.

The location of the ethylenic linkage in (III, R = H or O·CH_3) was not established with certainty, but the crimson colour of the 2 : 4-*dinitrophenylhydrazones* is characteristic of αβ-unsaturated ketones.

It is hoped that it will be possible to resume this investigation.

Experimental.

4-*Keto*-7-α-*naphthylheptoic Acid* (I, *n* = 2).—A mixture of γ-1-naphthylbutyric acid (20 g., prepared in 42% yield by malonic ester synthesis from β-1-naphthylethyl bromide), chloroform (100 c.c.), and pure thionyl chloride (18 c.c.) was refluxed for 2 hours, and the solvent and excess of thionyl chloride then evaporated. The acid chloride, dissolved in dry ether (60 c.c.), was slowly added, with shaking, to a solution of ethyl sodioacetylsuccinate prepared from powdered sodium (2·1 g.), ester (20 g.), and dry ether (200 c.c.), cooled in a freezing mixture. The mixture was allowed to reach room temperature after 2 hours, kept overnight, and then refluxed for 10 hours. The product (35·5 g.), isolated in the usual way, was shaken with aqueous potassium hydroxide (1000 c.c. of 4·5%) and alcohol (200 c.c.) for 24 hours; alcohol (100 c.c.) was then added, and shaking continued for 36 hours. Neutral material was removed with ether, and hydrolysis of the acidic portion completed by heating with 2N-sodium hydroxide (200 c.c.) on the steam-bath for 2 hours. The isolated acidic product (13·5 g.) was methylated by means of diazomethane (from 15 g. of nitrosomethylurea), and the ester obtained as a pale yellow, viscous oil (8·3 g.), b. p. 193—198°/0·4 mm., $n_D^{21°}$ 1·5685. Saponification gave the *keto-acid*, which, crystallised from ether–light petroleum (b. p. 60—80°) and then from ether, formed colourless needles, m. p. 123—124° (Found: C, 75·5; H, 6·7. $C_{17}H_{18}O_3$ requires C, 75·6; H, 6·6%). The *semicarbazone* crystallised from aqueous alcohol as a mat of silky needles and sintered with decomposition at *ca.* 170° (Found: C, 66·4; H, 6·3. $C_{18}H_{21}O_3N_3$ requires C, 66·1; H, 6·4%).

3′-*Keto*-3 : 4-*dihydro*-1 : 2-cyclo*pentenophenanthrene*.—Freshly prepared alcohol-free sodium ethoxide (0·5 g.) was added to a solution of methyl 4-keto-7-α-naphthylheptoate (1·1 g.) in ether (20 c.c.). The mixture was kept at room temperature for 20 hours, then refluxed on the steam-bath for ½ hour, cooled, and decomposed with ice and water. The aqueous layer, washed with some fresh ether and saturated with carbon dioxide, gave no precipitate. Dilute sulphuric acid was added, the precipitated gum extracted with ether and dried, and the solvent evaporated. The syrupy residue could not be crystallised; it was dissolved in moist benzene (120 c.c.), water (10 drops) added, and the solution refluxed. Phosphoric anhydride (10 g.) was gradually introduced into the boiling solution during 2 hours. The reaction mixture was cooled, and treated with ice and water. Sodium hydroxide (15 g.) was added to the aqueous layer, the alkaline solution extracted first with benzene and then with ether, and the extract dried and evaporated. The dark brown, sticky residue was dissolved in a mixture of benzene (40 c.c.)

and light petroleum (b. p. 60—80°) (10 c.c.), passed through a column of active alumina, and a fraction eluted with benzene (400 c.c.). The crystalline product obtained on removal of the solvent crystallised from alcohol (charcoal) in yellow scales (0·132 g.), m. p. 212—213°. Bardhan (J., 1936, 1848) gives m. p. 210°. The ketone formed a crimson 2 : 4-dinitrophenylhydrazone.

5-Keto-8-α-naphthyloctoic Acid (I, $n = 3$).—The method of preparation was that employed in the case of the lower homologue. γ-1-Naphthylbutyryl chloride from 19·1 g. of the acid was condensed with the sodio-derivative from powdered sodium (2·1 g.) and ethyl α-acetylglutarate (22 g.). The product (35·5 g.) was partly hydrolysed by shaking for 50 hours with aqueous potassium hydroxide (750 c.c. of 4·5%) and alcohol (350 c.c.). After hydrolysis had been completed with 2N-sodium hydroxide on the steam-bath, the crude mixture of acids (18·5 g.) was esterified with diazomethane. Fractionation yielded 9 g. of a pale yellow, somewhat viscous oil, b. p. 200—205°/0·4 mm., $n_D^{20°}$ 1·5625. The *keto-acid*, obtained on hydrolysis, crystallised from ether–light petroleum (b. p. 60—80°) in stout prisms, m. p. 66—67° (Found : C, 76·0; H, 7·2. $C_{18}H_{20}O_3$ requires C, 76·1; H, 7·0%). The *semicarbazone* crystallised from ethyl alcohol in colourless plates which sintered at *ca.* 148° (Found : N, 12·2. $C_{19}H_{23}O_3N_3$ requires N, 12·3%).

β-1′-*Naphthylethyl*cyclo*hexane*-2 : 6-*dione* (II).—Methyl 5-keto-8-α-naphthyloctoate (3 g.) in ether (25 c.c.) was treated with freshly prepared alcohol-free sodium ethoxide (1·2 g.) in the usual way. After keeping at room temperature for 24 hours, the reaction mixture was refluxed on the steam-bath for 30 minutes, treated with ice and water, and the alkaline aqueous layer washed once with ether and saturated with carbon dioxide. The fine precipitate was collected, washed with a little water, and crystallised from aqueous alcohol (60%), being obtained in colourless plates (1·7 g.), m. p. 199—200° (Found : C, 81·3; H, 6·9. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%). The product gave no coloration with alcoholic ferric chloride.

3-*Keto*-1 : 2 : 3 : 4 : 5 : 6-*hexahydrochrysene*.—Phosphoric anhydride (10 g.) was gradually added with occasional shaking, during 2 hours, to a boiling solution of β-1′-naphthylethyl*cyclo*hexane-2 : 6-dione (0·8 g.) in very damp benzene (150 c.c.). The reaction mixture was then cooled, ice and water added, and sodium hydroxide (20 g.) added to the aqueous layer. The benzene layer was separated, the aqueous alkaline solution extracted again with benzene, then twice with ether, and the combined extracts dried over sodium sulphate. On acidification of the alkaline aqueous layer, there was a considerable precipitation of unchanged diketone. The ether–benzene extract was evaporated and the brownish syrupy residue soon partly crystallised. It was recrystallised from alcohol (charcoal), being obtained in almost colourless leaflets, m. p. 154—156° (yield, 0·12 g. or 16%) (Found : C, 87·0; H, 6·5. $C_{18}H_{16}O$ requires C, 87·1; H, 6·4%).

When methyl 5-keto-8-α-naphthyloctoate (1·5 g.) was treated with phosphoric anhydride (15 g.) in very damp benzene (200 c.c.) under the above conditions, both ring closures occurred simultaneously, and from the neutral ketonic fraction of the reaction mixture the above ketohexahydrochrysene (0·162 g. after purification) was isolated.

The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark red prisms, m. p. 284° (decomp.) (Found : N, 13·2. $C_{24}H_{20}O_4N_4$ requires N, 13·1%).

Methyl 5-Keto-8-m-methoxyphenyloctoate.—γ-*m*-Methoxyphenylbutyryl chloride and ethyl sodio-α-acetylglutarate were condensed in a mixture of equal parts of benzene and ether, a slight excess of the ester being used. Hydrolysis was effected by shaking the condensation product (86 g.) with a solution of potassium hydroxide (44 g.) in water (1550 c.c.) for 10 hours. The alkali concentration was then raised to 4% by addition of potassium hydroxide (24 g.) and ethyl alcohol (150 c.c.), and shaking continued for 50 hours. The product was a pale yellow, viscous oil, b. p. 182—188°/0·25 mm. The average yield in five successive preparations was 41·9% and the best yield in a single run was 43·6%. In Part IX (Robinson and Walker, J., 1936, 747), a 25% yield was recorded.

γ-(6-*Methoxy*-3 : 4-*dihydro*-1-*naphthyl*)*butyric Acid*.—The methyl ester was obtained by the method of Part XV (Robinson and Walker, J., 1937, 60). The b. p. agreed with that previously recorded, 175—178°/0·2 mm., but not with that (157—158°/0·3 mm.) given by Chuang, Tien, and Huang (*Ber.*, 1937, **70**, 860). For the preparation of the acid the product of cyclodehydration of the keto-octoate was saponified without fractionation, and the crude acid crystallised from light petroleum (b. p. 60—80°). It formed colourless prisms, m. p. 79°, in agreement with Chuang, Tien, and Huang (*loc. cit.*) but not with the m. p. recorded in Part XV (*loc. cit.*). The substance described in that paper was doubtless partly dehydrogenated and the numerous crystallisations concentrated the naphthalene derivative.

β-(6′-*Methoxy*-1′-*naphthyl*)*ethyl*cyclo*hexane*-2 : 6-*dione*.—γ-(6-Methoxy-1-naphthyl)butyric

acid (8·2 g.), m. p. 149—150°, prepared in 75% yield by the dehydrogenation of the 3 : 4-dihydro-acid with sulphur and crystallised from aqueous acetone, was converted into the acid chloride and condensed in the usual way in benzene solution with ethyl sodio-α-acetylglutarate from the ester (10 g.) and powdered sodium (0·9 g.). The condensation product (15·7 g.) was shaken for 24 hours with potassium hydroxide (10 g.), water (250 c.c.), and alcohol (120 c.c.). As there was still a considerable amount of unhydrolysed oil, the alkali concentration was raised to 4·2% and shaking continued for 24 hours longer. Hydrolysis was completed by treatment with 2N-sodium hydroxide solution for 2 hours on the steam-bath, the crude mixture of acids methylated with diazomethane, and the esters dried in ethereal solution. Fractionation yielded only 3·85 g. of a deep yellow, viscous oil, b. p. 175—220°/0·2 mm., and there was a considerable tarry residue. In subsequent preparations, the crude mixture of acids was washed with hot water and methylated with diazomethane, and the esters dried in ethereal solution and used directly in the next stage. In this way γ-(6-methoxy-1-naphthyl)butyric acid (16 g.) and ethyl α-acetylglutarate (20 g.) gave crude methyl 5-keto-8-(6′-methoxy-1′-naphthyl)octoate (14·3 g.). To this crude keto-ester (7·5 g.) in ether (60 c.c.), freshly prepared alcohol-free sodium ethoxide (3·5 g.) was gradually added. After keeping at room temperature for 20 hours, the mixture was refluxed for 30 minutes, treated with ice and water, and the alkaline aqueous layer washed with ether and saturated with carbon dioxide. The precipitated diketone was taken up in much ether, and the extract dried over sodium sulphate, concentrated, and chilled; the diketone then crystallised (4·4 g.). It was recrystallised from ether in a similar manner, colourless needles (3·5 g.), m. p. 170—172°, being obtained. Chuang, Tien, and Huang (*loc. cit.*) give m. p. 168—170°.

3-*Keto*-10-*methoxy*-1 : 2 : 3 : 4 : 5 : 6-*hexahydrochrysene* (III, R = OMe).—Phosphoric anhydride (11 g.) was added gradually during 2 hours to a boiling solution of β-(6′-methoxy-1′-naphthyl)ethyl*cyclo*hexane-2 : 6-dione (1 g.) in very damp benzene (150 c.c.); refluxing was continued for 30 minutes. The product was isolated as in the case of the methoxyl-free compound. The crude material crystallised from alcohol in pale yellow plates (0·46 g.), m. p. 177—178° (Found : C, 81·8; H, 6·7. Calc. for $C_{19}H_{18}O_2$: C, 82·0; H, 6·5%). From three successive cyclodehydrations, 3·2 g. of the diketone gave 1·615 g. of the keto-chrysene, an average yield of 53·8%. Chuang, Tien, and Huang (*loc. cit.*) recorded a 21·2% yield. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in crimson prisms, m. p. 284° (decomp.) (Found : N, 12·4. $C_{25}H_{22}O_5N_4$ requires N, 12·2%). Hydrogen was not absorbed by this ketone in ethyl acetate or ethyl acetate–alcohol solution in the presence of palladised strontium carbonate catalyst. Approximately 3 mols. of hydrogen were absorbed comparatively rapidly when Adams's platinum oxide and an acetic acid solution were used. Analysis indicated that the main product was methoxyoctahydrochrysene, but it could not be fully purified.

p-*Nitrobenzoyl Derivative of* 3-*Hydroxy*-10-*methoxy*(or *ethoxy*)-1 : 2 : 3 : 4 : 5 : 6 : 15 : 16-*octahydrochrysene* (IV).—Sodium (2 g.) was added gradually during 1 hour to a boiling solution of the above ketone (0·47 g.) in absolute alcohol (15 c.c.). Alcohol (10 c.c.) was then added, and refluxing continued for 2½ hours. The glassy product was converted into a p-*nitrobenzoate* by treatment with *p*-nitrobenzoyl chloride (0·7 g.) and dry pyridine (3 c.c.) on the steam-bath for 3 hours. After removal of basic and acidic substances, the ester was twice crystallised from ethyl acetate; it formed yellow leaflets, m. p. 218—219° with softening from 214° (Found : C, 72·6; H, 6·4; N, 3·3. $C_{26}H_{25}O_5N$ requires C, 72·4; H, 5·8; N, 3·3. $C_{27}H_{27}O_5N$ requires C, 72·8; H, 6·1; N, 3·2%).

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