167. *The Effect of Steric Hindrance on the Course of Pfitzinger Reactions.*

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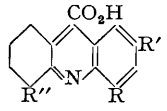
The Pfitzinger reactions between ketones, $R{\cdot}CH_2{\cdot}CO{\cdot}R'$, and various isatins have been shown to be subject to steric hindrance. On the other hand, it has been demonstrated that these condensations are not affected by choosing large molecules as reactants. In the course of the investigation, the hitherto unknown 10-propionyl-3 : 4-benzpyrene has readily been prepared, and its constitution determined.

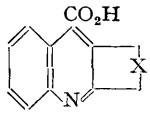
Although the condensation of isatin with ketones, $R{\cdot}CH_2{\cdot}CO{\cdot}R'$, has frequently been used for the synthesis of quinoline derivatives, attention has been paid to neither the steric nor the electronic factors likely to govern the reaction. Some previous isolated observations are consistent with the belief that steric hindrance may interfere with Pfitzinger's reaction. Borsche and Rottsieper (*Annalen*, 1910, **377**, 70) could not bring isatin into reaction with menthone, pulegone, or camphor, and von Braun (*Annalen*, 1927, **451**, 1) observed that tetrahydro-α-naphthisatin failed to react with α-tetralone. These authors, however, have not attempted to account for these remarkable failures.

The present paper forms part of a systematic investigation on the influence of various substituents upon the behaviour of ketones, $R{\cdot}CH_2{\cdot}CO{\cdot}R'$, towards isatin and its derivatives.

(a) *Steric Hindrance in the Ketonic Molecule.*—Isatin gave with 2-methyl*cyclo*hexanone the expected 1-*methyl*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic acid* (I; R = R′ = H; R″ = Me) in very high yield, and 2 : 3-meso*methyltrimethylenecinchoninic acid* (II) was similarly prepared from 3-methyl*cyclo*pentanone. In the

latter reaction, no evidence of the formation of an isomeric acid could be observed, as would be the case if no steric hindrance existed. On the other hand, we have been unable to detect any normal reaction between isatin and the following ketones: *iso*pulegone, dihydro*iso*pulegone, tetrahydrocarvone, and norcamphor. In

(I.) 

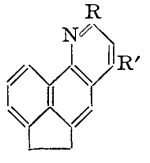


(II; X = CH_2·CHMe·CH_2)
(III; X = $[CH_2]_{13}$)

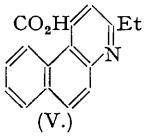
addition to menthone and camphor previously mentioned (Borsche *et al.*, *loc. cit.*), all these ketones bear substituents near both the carbonyl and the methylene group which would be involved in Pfitzinger's condensation. This conforms with the inability, already recorded by Borsche (*Ber.*, 1924, **57**, 1373), of dehydrocholic and dehydrodeoxycholic acid (as well as some other analogous derivatives of bile constituents) to react with more than one molecule of isatin. The suggested rule may perhaps be of value in the future for the elucidation of the configuration of natural products. 2 : 3-*Tridecamethylenecinchoninic acid* (III) has been obtained in almost theoretical yield from isatin and *cyclo*pentadecanone, thus indicating that an internal steric hindrance supposed by Angeli (*Gazzetta*, 1930, **60**, 939) to occur in the molecules of musk-smelling cyclanones does not apparently exist.

(b) *Steric Hindrance in the Isatin Molecule.*—The following examples show that the condensation proceeds normally when the part of the ketonic molecule involved in the reaction is not itself sterically hindered: 7 : 9-*dichloro*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic acid* (I; R = R′ = Cl, R″ = H) and 7 : 9-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic acid* (I; R = R′ = Me, R″ = H) have readily been obtained from 5 : 7-dichloro- and 5 : 7-dimethylisatin by interaction with *cyclo*hexanone.

α-Acenaphthisatin gave with acetone a cinchoninic *acid* (IV; R = Me, R′ = CO_2H) which yielded 3-methyl-8 : 9-ace-4-azaphenanthrene (IV; R = Me, R′ = H) on decarboxylation. The last substance had been obtained in another way by Nair and Simonsen (*J.*, 1926, 3140). Acetophenone and 2-acetylphenanthrene similarly yielded 3-*phenyl*-8 : 9-*ace*-4-*azaphenanthrene* (IV; R = C_6H_5, R′ = H) and 3-(2′-*phenanthryl*)-8 : 9-*ace*-4-*azaphenanthrene* (IV; R = $C_{14}H_9$, R′ = H) through the corresponding cinchoninic *acids* (IV; R′ = CO_2H).



(IV.)



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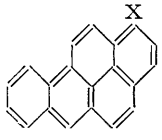
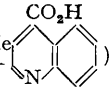


(VI; X = CO·Et)
(VII; X = )

(c) *Steric Hindrance in the Molecules of Both Partners.*—In this case, the reaction either fails, or takes an abnormal course: α- and β-Naphthisatins do not react with *cyclo*hexanone (Borsche and Wagner-Roemmich, *Annalen*, 1940, **544**, 274; Robinson and Bogert, *J. Org. Chem.*, 1936, **1**, 65). We have now found that α-acenaphthisatin follows that rule; furthermore, β-naphthisatin gives with methyl ethyl ketone 2-ethyl-1-azaphenanthrene-4-carboxylic acid (V), whereas isatin is known to afford under the same conditions 2 : 3-dimethylcinchoninic acid as the sole product (Pfitzinger, *J. pr. Chem.*, 1897, **56**, 283).

A significant proof of the ability of ketones of high molecular weight to react with isatin is provided by the synthesis of 2-(3′ : 4′-*benzpyrenyl*-10′)-3-*methylcinchoninic acid* (VII) from isatin and 10-*propionyl*-3 : 4-*benzpyrene* (VI). The last substance has readily been prepared from 3 : 4-benzpyrene, following a procedure devised by Windaus and Raichle (*Annalen*, 1939, **537**, 157) for the synthesis of the lower homologue; the constitution of (VI) has been ascertained by its conversion into 3 : 4-benzpyrene-10-carboxylic acid on oxidation by sodium hypobromite.

Some of the new substances recorded in this paper are being examined for carcinogenic activity.

Experimental.

1-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic Acid.*—A solution of isatin (10 g.), 2-methyl*cyclo*hexanone (15 g.), and potassium hydroxide (10 g.) in 50% ethanol (100 c.c.) was refluxed during 24 hours on a water-bath. The dark solution obtained was evaporated to half its bulk, twice shaken with ether in order to remove traces of methyl*cyclo*hexanone and other neutral products, and acidified with a slight excess of 50% acetic acid. The *acid* (10 g.) which separated on cooling was twice recrystallised from dilute alcohol, and then formed silky colourless needles, m. p. 267° (efferv.), almost insoluble in benzene, readily soluble in ethanol (Found: N, 6·0. $C_{15}H_{15}O_2N$ requires N, 5·8%).

2 : 3-meso*Methyltrimethylenecinchoninic Acid.*—Isatin (10 g.) and 3-methyl*cyclo*pentanone (20 c.c.) were treated as above with a solution of potassium hydroxide (10 g.) in 50% ethanol (100 c.c.). After acidification with acetic acid, a yellowish precipitate (11 g.) was formed; recrystallisation from benzene–alcohol afforded almost colourless needles of the *acid*, m. p. 277—278° (efferv.) (Found: N, 6·2. $C_{14}H_{13}O_2N$ requires N, 6·1%).

Attempts to Condense Isatin with Some Terpenic Ketones.—No appreciable reaction could be detected between isatin (10 g.) and *iso*pulegone, dihydro*iso*pulegone, tetrahydrocarvone, or norcamphor (15 g.) in the presence of potassium hydroxide (10 g. in 100 c.c. of 50% ethanol), even after 3 days' heating on a water-bath. No definite condensation product could also be obtained with the nitrogen-containing bicyclic ketone, tropanone; these failures cannot be attributed to decomposition of the ketones in the alkaline medium, as they could be recovered largely unchanged by extraction with ether.

2 : 3-*Tridecamethylenecinchoninic Acid.*—This *acid* was obtained in 90% yield when *cyclo*pentadecanone was allowed to react with isatin and potassium hydroxide in the usual manner. It crystallised from alcohol in fine glinting needles, m. p. 297—298° (efferv.), which were very soluble in acetic acid, and gave a tallowy base on decarboxylation (Found : N, 3·5. $C_{23}H_{31}O_2N$ requires N, 3·8%). No frothing occurred when aqueous solutions of its alkali salts were shaken.

7 : 9-*Dichloro*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic Acid.*—5 : 7-Dichloroisatin (7·5 g.) was treated with *cyclo*hexanone (10 g.) and potassium hydroxide (10 g.) in aqueous ethanol (80 c.c.) during 24 hours. The *acid* thus obtained crystallised from *iso*propanol in glistening colourless needles (12 g.), m. p. 302—303° (efferv.), which were almost insoluble in cold ethanol or benzene (Found : N, 4·6. $C_{14}H_{11}O_2NCl_2$ requires N, 4·7%).

7 : 9-*Dimethyl*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic Acid.*—This *acid*, obtained from 5 : 7-dimethylisatin (5 g.) and *cyclo*hexanone (10 g.), formed silky colourless needles, m. p. 247—248° (11 g.), which were fairly soluble in alcohol (Found : N, 5·7. $C_{16}H_{17}O_2N$ requires N, 5·5%). The high yields recorded in this and the foregoing experiment indicate that the amino-groups of both isatins are not sterically hindered.

3-*Methyl*-8 : 9-*ace*-4-*azaphenanthrene*-1-*carboxylic Acid.*—A solution of α-acenaphthisatin (2·2 g.; cf. Langenbeck, Hellrung, and Jüttemann, *Annalen*, 1934, **512**, 276; Buu-Hoï and Hiong-Ki-Wei, *Rev. sci.*, 1944, **82**, 168), acetone (3 c.c.), and potassium hydroxide (3 g.) in aqueous ethanol (30 c.c. of ethanol, 3 c.c. of water) was refluxed during 30 hours on a water-bath. The *acid* thus obtained (2·1 g.) crystallised from alcohol in slender yellowish prisms, m. p. 302° (efferv.) (Found : N, 5·1. $C_{17}H_{13}O_2N$ requires N, 5·0%). It afforded, on decarboxylation and subsequent vacuum-distillation, 3-methyl-8 : 9-ace-4-azaphenanthrene, m. p. 130—131° (Nair and Simonsen, *loc. cit.*, give m. p. 131°). The *hydrochloride* of this base crystallised from dilute hydrochloric acid in long silky bright yellow needles (Found : N, 5·5. $C_{16}H_{13}N,HCl$ requires N, 5·5%).

3-*Phenyl*-8 : 9-*ace*-4-*azaphenanthrene.*—3-*Phenyl*-8 : 9-*ace*-4-*azaphenanthrene*-1-*carboxylic acid* was obtained in 85% yield from α-acenaphthisatin and acetophenone; it crystallised from ethanol in slender yellowish prisms, m. p. 278—279° (efferv.) (Found : N, 4·1. $C_{22}H_{15}O_2N$ requires N, 4·3%). Vacuum distillation produced the corresponding *base*, which crystallised from alcohol–benzene in clumps of silky yellowish needles, m. p. 157° (Found : N, 5·2. $C_{21}H_{15}N$ requires N, 5·0%). Concentrated sulphuric acid produced a deep yellow coloration, and the alcoholic solutions displayed an intense greenish-blue fluorescence; treatment with picric acid gave a molecular complex, which separated from alcohol in long, silky, orange-yellow needles, m. p. 154—155° (decomp.).

3-(2′-*Phenanthryl*)-8 : 9-*ace*-4-*azaphenanthrene.*—The corresponding cinchoninic *acid* was obtained in 80% yield from α-acenaphthisatin and 2-acetylphenanthrene (Mosettig and van der Kamp, *J. Amer. Chem. Soc.*, 1930, **52**, 3704). It crystallised from boiling *iso*amyl alcohol as a yellowish microcrystalline powder which decomposed above 310° (Found : N, 3·1. $C_{30}H_{19}O_2N$ requires N, 3·3%). The aqueous solutions of its sparingly soluble salts with alkali metals give a very persistent foam. The corresponding *base* could be distilled without decomposition, and crystallised from benzene in slight yellowish needles, m. p. 248°, which were very sparingly soluble in alcohol; its solutions in concentrated sulphuric acid were deep yellow and showed an intense green fluorescence (Found : N, 3·5. $C_{29}H_{19}N$ requires N, 3·6%). The picrate was very unstable.

2-*Ethyl*-1-*azaphenanthrene*-4-*carboxylic Acid.*—A solution of β-naphthisatin (2 g.), methyl ethyl ketone (2 c.c.), and potassium hydroxide (2·8 g.) in aqueous ethanol (25 c.c. of ethanol, 2 c.c. of water) was refluxed for 24 hours on a water-bath. The standard treatment gave a cinchoninic acid which crystallised from ethanol in almost colourless silky needles, m. p. 292—293° (efferv.). Doebner and Felber (*Ber.*, 1894, **27**, 2021) record m. p. 283° for the acid prepared by heating propaldehyde, β-naphthylamine, and pyruvic acid. Decarboxylation of our acid gave 2-ethyl-1-azaphenanthrene, m. p. 61° (Doebner and Felber gave m. p. 63°); the *picrate* of this base separated from alcohol in fine yellow needles, m. p. 172—173°, which were extremely soluble in benzene and hot alcohol (Found : N, 13·2. $C_{15}H_{13}N,C_6H_3O_7N_3$ requires N, 12·8%). The presence of the ethyl group accounts for the abnormally low m. p. of the picrate.

10-*Propionyl*-3 : 4-*benzpyrene.*—A solution of 3 : 4-benzpyrene (1·5 g.) in carbon disulphide (50 c.c.) was slowly added to an ice-cooled solution of aluminium chloride (1·5 g.) in propionyl chloride (10 g.). A somewhat violent reaction took place, and the mixture obtained was kept at room temperature for two hours and then poured into dilute hydrochloric acid; the sticky brownish semi-solid mass which separated was extracted with chloroform, the organic layer washed with dilute alkali and with water and dried ($MgSO_4$), and the solvent removed. The solid *residue* was crystallised four times from alcohol–benzene, giving short bright yellow needles, m. p. 125—126°, which dissolved in sulphuric acid with an intense violet coloration (Found : C, 89·4; H, 5·0. $C_{23}H_{16}O$ requires C, 89·6; H, 5·2%). The yield in this experiment (1·5 g.) was somewhat higher than that observed by Windaus and Raichle (*loc. cit.*) for acetylbenzpyrene. This is obviously due to the lesser reactivity of propionyl chloride which prevents it from giving a diketonic by-product. The acid obtained from propionylbenzpyrene and an alkaline solution of sodium hypobromite gave a methyl ester, m. p. 178—179° (Windaus and Raichle give m. p. 181° for the methyl ester of 3 : 4-benzpyrene-10-carboxylic acid).

2-(3′ : 4′-*Benzpyrenyl*-10′)-3-*methylcinchoninic Acid* (VII).—A mixture of 10-propionyl-3 : 4-benzpyrene (0·3 g.), isatin (0·15 g.), and potassium hydroxide (0·2 g. in a few drops of water) was heated with ethanol (25 c.c.) during 24 hours. The cooled mixture was twice extracted with hot xylene after dilution with water, and the aqueous layer acidified with acetic acid. The *acid* (0·3 g.) thus precipitated crystallised from nitrobenzene in deep yellow microscopic needles, m. p. 325—326° (efferv.) (Found : N, 3·1. $C_{31}H_{19}O_2N$ requires N, 3·2%). Sulphuric acid produced an intense purple-red coloration, which rapidly became violet.

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