QUININDINES

I. The Synthesis of 2,3-Dihydro-β-quinindines (β-Quinindanes) by the Pfitzinger Reaction

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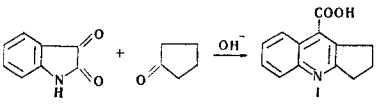
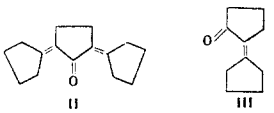
It is shown that, together with β-quinindane-9-carboxylic acid, the condensation of isatin with cyclopentanone in alkaline medium (Pfitzinger reaction) also affords α,α'-dicyclopentylidenecyclopentanone and 3-cyclopentylidene-β-quinindane-9-carboxylic acid, the structure of which was confirmed by its NMR, IR, and UV spectra.

One of the principal methods of obtaining β-quinindines (cyclopenta[b]quinolines) is by the Pfitzinger condensation of isatin with cyclopentanone, carried out in alkaline solution. This reaction was first utilized by Borsche [1], and subsequently by several other workers [2–5]. The method involves dissolving the salt of β-quinindane-9-carboxylic acid (we propose to call 2,3-dihydro-1H-cyclopenta[b]quinoline (or 2,3-dihydro-β-quinindine) by the name β-quinindane), and separating it from the copious residual solid. We have examined the by-products from this reaction. One of them (mp 78–80° C), which is soluble, unlike the others, in dichloroethane, benzene, and ether,



I

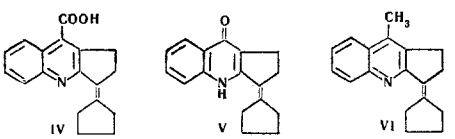
but insoluble in acids and alkalis, has the molecular formula $C_{10}H_{14}O$. The IR spectrum of this compound displays bands corresponding to a C=C double bond, and to a carbonyl group conjugated with a double bond. On the basis of these observations, we attribute to this compound the structure α,α'-dicyclopentylidenecyclopentanone (II). According to the literature [6], II has mp 76–77° C, and is obtained by the self-condensation of cyclopentanone in alkaline medium, together with α-cyclopentylidenecyclopentanone (III). The formation of II in the reaction, if allowed for, requires nearly a threefold excess of cyclopentanone.



II III

The other by-product which was isolated has the molecular formula $C_{18}H_{16}NO_2 \cdot H_2O$ (the molecule of water is lost in vacuo at 75° C over P_2O_5). In contrast to the acid I, it is soluble in methanol and acetone, forms a hydrochloride, and is soluble in dilute alkalis (the Na or K salt separates from concentrated alkalis). Unlike compound I, the alkaline solution of the compound instantaneously decolorizes potassium permanganate solution in the cold. The UV spectrum (Fig. 1) shows a considerable shift of the absorption bands to longer wavelengths in comparison with the bands in the spectrum of the acid I. All these results permit the assignment of the structure 3-cyclopentylidene-β-quinindane-9-carboxylic acid (IV) to the compound. The yield of acid IV amounted to 15%, and the acid I to 62%, calculated on the isatin used. Treatment of the acid IV with diazomethane gave the methyl ester.

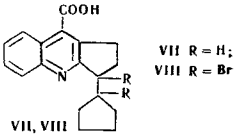
Compound IV is apparently formed as a result of the condensation of isatin with the by-product ketone III, since I does not react with cyclopentanone, as was shown in a special experiment under similar conditions (boiling in aqueous-alcoholic alkali).



IV V VI

The formation of the acid **IV** which we have observed is analogous to the previously described [7] formation of V. Condensation of anthranilic acid with cyclopentanone at 265° C (Tidke reaction) gives, instead of the expected 2,3-dihydro-1H-cyclopenta[b]quinoline-9-one, compound V, the formation of which the authors also incline to consider as the result of the condensation of anthranilic acid with the ketone III which is formed as an intermediate. Compound VI was obtained [8] by the Friedlander reaction, involving the direct condensation of the ketone III with o-aminoacetophenone.

The double bond in the acid IV is extremely reactive. It was hydrogenated at 45–50° C in acetic acid, using palladium-charcoal catalyst, and bromine added to the double bond in acetic acid in the presence of sodium acetate. It should be pointed out that the UV spectra of the product of hydrogenation product, 3-cyclopentyl-β-quinindane-9-carboxylic acid (VII), and of the bromination product, 3-bromo-3-(1'-bromocyclopentyl)-β-quinindane-9-carboxylic acid (VIII), as would be expected, resemble closely the UV spectrum of the acid I (Fig. 1).



The structure of IV was confirmed by its IR and NMR spectra.

The IR spectrum of IV showed bands characteristic of the COOH group: 1690 cm^{-1} ($\nu_{C=O}$), and a series of small bands in the 2500–2800 cm^{-1} region (OH group, valency stretching, and complex bands). It may, therefore, be concluded that IV, as opposed to I (the IR spectrum of I indicates that it has the betaine structure: ν_{COO^-} 1610, 1410 cm^{-1}, the $\overset{+}{N}H$ group gives rise to wide bands of medium intensity: 2450 cm^{-1} (the "ammonium band") and 2050 cm^{-1} (the "amine salt" band), whilst the C=O bond disappears, to reappear ($\nu_{C=O}$ 1730 cm^{-1}) in the IR spectrum of the hydrochloride of I) exists not only as the betaine, but also in the form with stable intermolecular hydrogen bonds of the type $\gtrless N \cdot\cdot HO-\overset{\overset{O}{\|}}{C}-\lessgtr$, which are characteristic of the pyridine- and quinoline-carboxylic acids [9]. This can only be explained in terms of steric hindrance. The molecular skeleton of IV, judging from molecular models (Framework Molecular Models, USA), is almost planar (atoms C-11 and C-12 constitute partial exceptions). The hydrogen atoms at C-10 are therefore in close proximity to the nitrogen atom and block it. They themselves, in turn, are influenced by the aromatic quinoline ring, in agreement with the NMR findings (see below). On the other hand, the IR spectrum of the hydrogenated compound VII indicates the formation of simple intermolecular hydrogen bonds, such as occur in the quinolinecarboxylic acids. In this case, the 3-cyclopentyl substituent is located outside the plane of the quinindane, and access to the N-atom is facilitated.

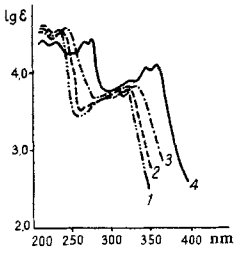


Fig. 1. UV Spectral in alcoholic solution: 1) β-quinindane-9-carboxylic acid (I); 2) 3-cyclopentyl-β-quinindane-9-carboxylic acid (VII); 3) 3-bromo-3-(1'bromocyclopentyl)-β-quinindane-9-carboxylic acid (VIII); 4) 3-cyclopentylidene-β-quinindane-9-carboxylic acid (IV).

The NMR spectrum of IV was recorded in trifluoroacetic acid and in dilute NaOD in D_2O (see table). The spectrum in trifluoroacetic acid (Fig. 2) contains (as also does I), bands corresponding to the four protons of the benzene ring in the quinoline system; a doublet with J = 7 Hz at 8.56 ppm (proton at C-5), and a multiplet at 7.8–8.4 ppm (protons at

C-6, C-7, and C-8). At higher field there are found four very wide lines (mainly from 25-40Hz wide) with centers at 2.11, 2.79, 3.16 and 3.65 ppm corresponding to the absorption of four, two, four, and again two protons. These lines must be due to the protons of the six methylene groups. The signal at highest field (2.11 ppm, four protons) may be attributed to the superimposed absorption of the methylene protons at C-11 and C-12 which are less deshielded by double bonds than the protons of the other methylene groups.

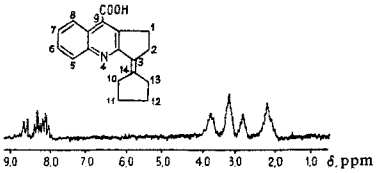


Fig. 2. NMR Spectrum of 3-cyclopentylidene-β-quinindane-9-carboxylic acid (IV) in trifluoroacetic acid.

The signal at lowest field (3.65 ppm) is apparently due to the protons of the methylene group at C-10. On the one hand, this adjoins an atom with a substantial deficiency of electrons (resulting from conjugation of the double bond with the pyridine ring), and on the other hand, it has already been pointed out that the protons of this group (as distinct from the protons at C-13), are in immediate juxtaposition to the nitrogen atom of the quinoline ring. This makes it possible for the ring current of the quinoline ring, and also the anisotropy of the C=N bond, to influence these protons.

Chemical Shifts (δ) in NMR Spectra (ppm)

Compound	Solvent	Protons on					
		C-1	C-2	C-3	C-10	C-11 C-12	C-13
I	CF_3COOH	3.11**	2.10***	3.18**	—	—	—
Methyl ester of IV*	CF_3COOH	3.13	3.13		3.52	2.11	2.79
IV	CF_3COOH	3.16	3.16		3.65	2.11	2.79
IV	$NaOD/D_2O$	2.81	2.81		3.01	1.76	2.38
$\Delta\delta_{IV}$****		0.35	0.35		0.64	0.35	0.41

*The singlet due to the methyl group of CH_3OCO occurs at 4.32 ppm.
**The protons at C-1 and C-3 in I give two partially superimposed triplets.
***Quintet
****Differences in the values of the chemical shifts of IV in CF_3COOH and in $NAOD/D_2O$.

Information which is useful for the assignment of the signals is obtained by comparing the spectra of IV in trifluoroacetic acid and in a solution of NaOD in D_2O. The protons which are the most sensitive to protonation of the nitrogen atom must be those at C-10 and C-13, since these methylene groups adjoin the end of the conjugated chain at C-14. The signal at 3.65 ppm shows the largest shift (see table), which supports its assignment to the protons at C-10. Further, the signal at 2.79 ppm may, on this basis, be assigned to the protons at C-13. The absorption of the protons at C-1 in IV is apparently a component of the signal at 3.16 ppm, since this signal is close in chemical shift to the signal of the methylene group at C-1 in the acid I. As far as the other two protons are concerned, the absorption of which forms part of this (3.16 ppm) signal, these must be the protons at C-2, since the other protons have all been assigned. The chemical shifts of the protons at C-1 and C-2 are similar, and these protons give a single combined, unresolved signal.

EXPERIMENTAL

The condensation of isatin with cyclopentanone. A mixture of 50 g (0.33 mole) of isatin, 400 ml of ethanol, 200 ml of 33% aqueous potassium hydroxide, and 85 g (0.95 mole) of cyclopentanone was boiled under reflux for 8.5 hr, and the ethanol and part of the water was then removed in vacuo (about 350 ml in all). The residue was diluted with 800 ml of water (addition of a smaller amount of water resulted in the potassium salt of the acid IV remaining undissolved, as

in [1]), and extracted with 300 ml of dichloroethane. The dichloroethane solution was treated with activated charcoal, dried over magnesium sulfate, and evaporated in vacuo. The residual oil was rubbed with light petroleum, giving 8.5 g of α, α'-dicyclopentylidenecyclopentanone (II) which after recrystallization from light petroleum had mp 78–80° C (lit. [6], 76–77° C). Found, %: C 83.29; H 9.41. Calculated for $C_{15}H_{20}O$, %: C 83.28; H 9.32.

The aqueous layer, after treatment with activated charcoal, was acidified with glacial acetic acid to pH 6, with cooling. The precipitate which separated was filtered off, washed a few times with water, and extracted with acetone (5 × 100 ml). Evaporation of the acetone and recrystallization from 60% aqueous ethanol gave 16 g (15%, calculated on isatin) of 3-cyclopentylidene-β-quinindane-9-carboxylic acid (IV) monohydrate, mp 113–115° C (decomp.). Found, %: C 72.60; H 6.44; N 4.91; H_2O 5.95. Calculated for $C_{18}H_{17}NO_2 \cdot H_2O$, %: C 72.71; H 6.44; N 4.71; H_2O 6.06. The anhydrous material, mp 198–200° C (decomp.), was obtained by drying over P_2O_5 at 75° C (15 mm) for 3 hr. Found, %: C 77.70; H 6.17; N 5.21. Calculated for $C_{18}H_{17}NO_2$, %: C 77.40; H 6.13; N 5.01. UV spectrum, λ_{max}, nm (lg ε): 229 (4.39), 265 (4.37), 273 (4.39), 326 (3.69) shoulder, 341 (4.06), and 356 (4.09).

The methyl ester of acid IV was obtained by treating the aqueous-methanolic solution of the monohydrate of IV with ethereal diazomethane, mp 135–136° C (from methanol). Found, %: C 77.51; H 6.39; N 4.84. Calculated for $C_{19}H_{19}NO_2$, %: C 77.79; H 6.53; N 4.77.

The hydrochloride of acid IV mp 190–192° C (decomp., from 10% HCl and from absolute ethanol). Found, %: C 68.51; H 5.86; N 4.43; Cl 11.06. Calculated for $C_{18}H_{17}NO_2$, %: C 68.45; H 5.74; N 4.44; Cl 11.23. The IR spectrum showed ν_{CO} at 1710 cm^{-1}.

The residue left after extraction with acetone was β-quinindane-9-carboxylic acid (I), mp 280–282° C (decomp.) (lit. [1], 277–278° C), yield 45 g (62% calculated on the isatin). UV spectrum, λ_{max}, nm (lg ε): 234 (4.52), 297 shoulder (3.70), 307 (3.76), 320 (3.80). Hydrochloride of I, mp 240° C (decomp., from alcohol). Found, %: Cl 14.34. Calculated for $C_{13}H_{11}NO_2 \cdot HCl$, %: Cl 14.20.

3-Cyclopentyl-β-quinindane-9-carboxylic acid (VII). A solution of 1.50 g of 3-cyclopentylidene-β-quinindane-9-carboxylic acid (IV) monohydrate in 30 ml of glacial acetic acid was hydrogenated over 0.15 g of 10% palladium on charcoal at atmospheric pressure and 45–50° C for 5 hr. The catalyst was filtered off, water added, and the precipitate which separated was extracted with ether, the extract washed with water, and the solvent removed in vacuo. The residue was triturated with water and compound VII filtered off, mp ~240° C (decomp., from alcohol). Yield 0.8 g. Found, %: C 76.63; H 6.55; N 5.12. Calculated for $C_{18}H_{19}NO_2$, %: C 76.85; H 6.81; N 5.00. The IR spectrum showed bands at 1610 and 1400 cm^{-1} (COO^-), and at 2050 and 2550 cm^{-1} ($\rangle NH^+$). UV spectrum, λ_{max}, nm (lg ε): 234 (4.56), 295 shoulder (3.71), 308 (3.75), and 321 (3.80).

3-Bromo-3-(1'-bromocyclopentyl)-β-quinindane-9-carboxylic acid (VIII). To a mixture of 5 g of IV, 1.7 g of anhydrous sodium acetate, and 30 ml of glacial acetic acid was added over 1 hr at 10° C a solution of 1.4 g of bromine in 5 ml of glacial acetic acid, stirred for 1 hr at room temperature, the precipitate filtered off and washed on the filter with water and with acetone to give 5.1 g, mp 115–118° C (decomp., reprecipitated from dimethylformamide by adding water). Found, %: C 49.84; H 4.05; Br 36.26. Calculated for $C_{18}H_{16}Br_2NO_2$, %: C 49.35; H 3.68; Br 36.49. The IR spectrum showed bands characteristic for the carboxyl group (ν_{CO} 1692 cm^{-1}), and for OH (several small bands at 2500–2800 cm^{-1}).

UV spectra were taken in alcoholic solution on a Hitachi (Japan) recording spectrophotometer, and the IR spectra as suspensions in vaseline oil on the UR-10 spectrograph. The NMR **spectra** were taken on a JNM-4H-100 spectrometer with a working frequency of 100 MHz (JEOL, Japan), using as internal standards hexamethylsiloxane (in trifluoroacetic acid) and tert-butanol (in $NaOD/D_2O$), the values of the chemical shifts being calculated with respect to tetramethylsilane.

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