# Synthesis of Substituted Octahydroindolo[2,3-*a*]quinolizines. The Formation of a New Type of Ring System

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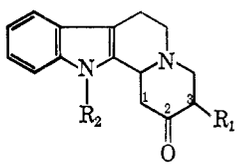
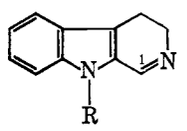
The reaction of $\alpha,\beta$-unsaturated ketones with 3,4-dihydro-$\beta$-carboline was investigated. The main products of these reactions are octahydro-2-oxoindolo[2,3-*a*]quinolizines, or derivatives of a new type of ring system (IV), according to the conditions used. The structure of ring skeleton IV is supported by physical and chemical investigations.

A convenient synthesis of substituted octahydro-2-oxoindolo[2,3-*a*]quinolizines (I), key intermediates in the synthesis of many indole alkaloids, was effected by reaction of 3,4-dihydro-$\beta$-carboline (IIa) with $\alpha,\beta$-unsaturated ketones.[1-6]

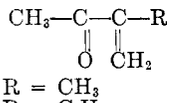
Compound Ib, an important intermediate for the formation of dihydrocorynantheine-type alkaloids, was obtained from butenone IIIb and IIa by heating the reactants in refluxing ethanol for 6 hr with a catalytic amount of HCl. When the reaction was allowed to proceed at room temperature in the absence of acid the crystals of another compound (IVb) precipitated from the solution and only a small amount of Ib was isolated from the mother liquor. Compound IVb was also obtained when hot benzene was used as solvent.



Ia, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = C_2H_5$; $R_2 = H$
c, $R_1 = n\text{-}C_3H_7$; $R_2 = H$
d, $R_1 = i\text{-}C_4H_9$; $R_2 = H$
e, $R_1 = CH_2C_6H_5$; $R_2 = H$
f, $R_1 = CH_2COOCH_3$; $R_2 = H$
g, $R_1 = CH_2CH_2COOCH_3$; $R_2 = H$
h, $R_1 = C_2H_5$; $R_2 = CH_3$



IIa, R = H
b, R = $CH_3$



IIIa, R = $CH_3$
b, R = $C_2H_5$
c, R = $n\text{-}C_3H_7$
d, R = $i\text{-}C_4H_9$
e, R = $CH_2C_6H_5$
f, R = $CH_2COOCH_3$
g, R = $CH_2CH_2COOCH_3$

The solubilities of the two products (Ib and IVb) in alcohol were different, but they possessed very similar ultraviolet and infrared spectra and nearly identical melting points and both could be oxidized to the same product in acetic acid solution by the means of mercury(II) acetate. On the basis of these properties and because of a faulty nitrogen analysis we believed them at first to be stereoisomers.[6]

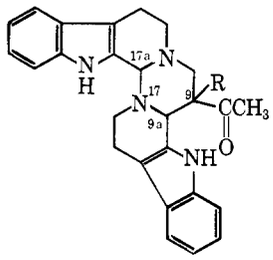
The structure of compound Ib has been definitely established through its reduction to known oxygen-free derivative V in good yield by means of the Wolff–Kishner method.[7] The latter product (V) was dehydrogenated to the alkaloid flavopereirine.[6,7]

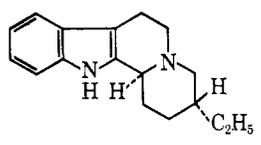
On the other hand ketone IVb was not convertible under the same conditions to the aformentioned products. Furthermore the nmr spectra of Ib and IVb showed such great differences that the "stereoisomer" hypothesis was untenable.

The analysis of further derivatives and the molecular weight determinations clearly revealed that derivatives IVa–e were formed by the reaction of 2 moles of dihydro-$\beta$-carboline (IIa) with 1 mole of unsaturated ketone III. This is evident also from the integration of nmr spectra.

The signal from the methyl group protons of compound Ib with proved structure appeared at $\delta$ 0.96, whereas the methyl group signal of IVb appeared at much lower frequency ($\delta$ 0.42) presumably owing to the long-range shielding effect of the aromatic indole nucleus. The signal from the protons of the acetyl group of IVb ($\delta$ 2.18) is entirely missing from the spectrum of Ib. The two angular protons give signals at $\delta$ 4.43 and 4.71, respectively. The protons of the NH groups appear at $\delta$ 8.0 and 8.68, respectively; however in deuteriopyridine solution these two signals coalesce at $\delta$ 8.32.

The nmr spectral data of other derivatives (see the Experimental Section) substantiate the shown structure IVa–e; *e.g.*, in the case of IVa one can find the signal





IVa, R = $CH_3$
b, R = $C_2H_5$
c, R = $n\text{-}C_3H_7$
d, R = $CH_2COOCH_3$
e, R = $CH_2CH_2COOCH_3$

V

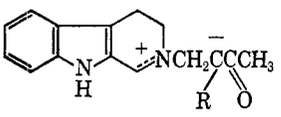
of the methyl group at $\delta$ 1.33. Because of a shorter distance to the pyrimidine ring this group is in the deshielding region of the indole nucleus, unlike the methyl groups of IVb and IVc.

(1) C. Szántay and L. Töke, *Tetrahedron Letters*, 251 (1963).
(2) A. Brossi, K. H. Chopard-dit-Jean, J. Würsch, and O. Schnider, *Helv. Chim. Acta*, **43**, 583 (1960).
(3) D. Beke and C. Szántay, *Chem. Ber.*, **95**, 2132 (1962); *Magy. Kém. Folyoirat*, **68**, 426 (1962).
(4) C. Szántay and J. Rohály, *ibid.*, **98**, 557 (1965); **70**, 478 (1964).
(5) C. Szántay and J. Rohály, *ibid.*, **96**, 1788 (1963); **69**, 390 (1963).
(6) C. Szántay and L. Töke, *Acta Chim. Hung.*, **39**, 249 (1963).
(7) E. Wenkert and B. Wieckberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).

The ultraviolet spectra (the ratio of log $\epsilon$ values) and the infrared spectral data are also in harmony with the discussed structure (IV).

Catalytic hydrogenation of IVb led to 1,2,3,4-tetrahydro-$\beta$-carboline and VIa. The latter compound was synthesized in an independent way, by treating the 1,2,3,4-tetrahydro-$\beta$-carboline with unsaturated ketone IIIb.

Formation of ring system IV can be explained as follows. During the addition of the basic nitrogen atom of $\beta$-carboline derivative II to the double bond of ketone III, zwitterion VII forms and it can undergo stabilization by a 1,4-dipole cycloaddition process[8] to the C=N bond of a free 3,4-dihydro-$\beta$-carboline (IIa) molecule.[9]



VII

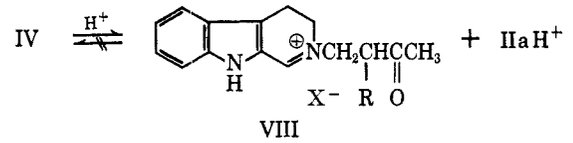
This mechanism is supported by results of studies of the reaction of base II with other unsaturated ketones (III).

If the ketones have unbranched substituents attached to the double bond (IIIa–c, f, g), reaction occurs entirely according to the pattern given above. In cold alcohol or in aprotic solvent at higher temperature, derivatives of IV are obtained as chief products. In boiling alcohol, however, only products having structure I could be isolated. *If the unsaturated ketone (III) has a branched substituent* (IIId, e), in cold or warm alcohol as well as in aprotic solvent *quinolizine derivative I is formed exclusively* because of steric effects. Furthermore the N-methyl-3,4-dihydrocarboline (IIb) undergoes reaction with ketone IIIb to produce only Ih, even at low temperatures.

Formation of indolo[2,3-*a*]quinolizine derivatives (I) proceeds by the same mechanism as the formation of benzo[*a*]quinolizine derivatives;[4] *i.e.*, the ring closure of VII requires the proper enolate.

In contrast to the behavior of I, ring system IV opens up rapidly and irreversibly even under the influence of dilute acid and gives the appropriate immonium salt (VIII). Under similar conditions compounds I are totally stable, opening slightly and reversibly[4] on heating with concentrated acids.

Table I shows the quantitative parameters for the process shown.



VIII

It is evident from the data of Table I that the bulkier the R group the more strained the ring system IV which results in higher reaction rates and lower activation enthalpies.

(8) R. Huisgen and K. Herbig, *Ann.*, **688**, 98 (1966).

(9) It is to emphasize that prior to this investigation the same process was observed and thoroughly investigated in the case of reactions between 3,4-dihydroisoquinoline derivatives and $\alpha,\beta$-unsaturated ketones: see L. Novák, Dissertation, 1966; C. Szántay and L. Novák, Lecture in the Symposium of the Hungarian Chemical Society, Sopron, 1965.

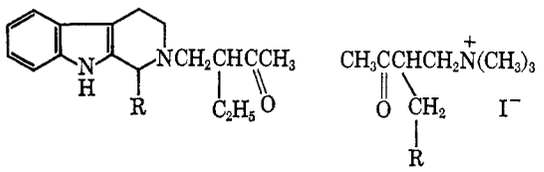
TABLE I

THE HALF-TIMES AND ACTIVATING PARAMETERS OF THE PROCESS IV ⟶ VIII + IIaH$^+$ AT 25 ± 0.01° IN 0.001 *N* HYDROCHLORIC ACID

| Compd | Half-time, sec | *H*, kcal/mole | *S*, cal/mole |
|---|---|---|---|
| IVa | 205[a] | 21.1 | +1.1 |
| IVb | 130 | 21.6 | +3.5 |
| IVd | 57 | 17.8 | −7.3 |
| IVe | 27 | 17.1 | −6.8 |

[a] Measured at 10 ± 0.01°.

Immonium salt VIII (R = $C_2H_5$, X = $ClO_4$) was isolated from the reaction mixture. It was convertible to pseudo-base VIb in basic medium and could be reduced catalytically to tetrahydro derivative VIa.



VIa, R=H
b, R=OH

IXa, R=$CH_2COOCH_3$
b, R=$COOCH_3$

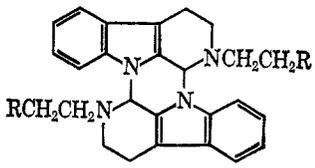
Salt VIII (R = $C_2H_5$, X = $ClO_4$) is convertible to derivative Ib under the influence of either acid or base; *i.e.*, the complete reaction sequence is IV → VIII → I.

The latter reaction also explains the fact that the mercury(II) acetate oxidation process leads to the same product with both IVb and Ib.[6]

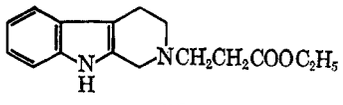
The isolation of salt VIII enabled us to make additional experiments to substantiate the above-described mechanism of the formation of ring system IV. One equivalent of base was given to the solution containing 1 equiv of salt VIII (R = Et) and base IIa. By working up the reaction mixture after a few hours, compound IVb was isolated. This latter procedure was performed earlier by us to prove the mechanism of forming of compounds with analogous structure in the isoquinoline series.[9]

It is worth mentioning that ketocarboxylic acid ester Ig could also be obtained by boiling compound IIa with quaternary salt IXa in alcohol.[10]

The observation of the reaction of $\alpha,\beta$-unsaturated ketones III with compound IIa leading to structure IV stimulated us to investigate the reaction of 3,4-dihydro-$\beta$-carboline with other reagents containing activated double bonds. However, on carrying out the reaction with acrylic acid ester or acrylonitrile, a new reaction pattern leading to products Xa and Xb was observed.



Xa, R=$COOC_2H_5$
b, R=CN



XI

(10) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1449 (1963).

The preparation of compounds with similar structures by quaternization of compound IIa with methyl iodide followed by alkylization was reported by Gupta and Spencer.[11]

The NH peak is absent in the infrared spectra of compounds Xa and Xb. Under the influence of acids they split into the corresponding monomeric immonium salt immediately. Catalytic hydrogenation yields tetrahydro-β-carboline derivative XI. After recrystallization of Xa from a mixture of dioxane and $D_2O$ its infrared spectrum remains unchanged demonstrating the absence of the acidic NH bond.

Finally we wish to mention that, of the compounds synthesized as described above, derivative Ig was used for the synthesis of β-yohimbine and yohimbine,[12] and derivative Ib for producing flavopereirine.[6] Experiments in progress aim to utilize compounds Ib and If in the syntheses of dihydrocorynantheine-, corynantheine-, and heteroyohimbane-type of ring structures. These experiments support the usefulness of compounds with structure I as intermediates for the synthesis of a wide group of indole alkaloids.

## Experimental Section

Concerning the preparation of unsaturated ketones IIIa–e, see ref 3, 5, and 13. 3,4-Dihydro-β-carboline (IIa) was obtained in crude form from N-formyltryptamine in 85.5% yield[14] and it could be used for the next reaction steps without any further purification.

**4-Methylene-5-oxocapronic Acid Methyl Ester (IIIg) and 4-Dimethylaminomethyl-5-oxocapronic Acid Methyl Ester Methyl Iodide (IXa).**—A suspension of 138 g (0.6 mole) of α-acetylglutaric acid diethyl ester[15] in 1200 ml of 1 *N* NaOH solution was stirred vigorously for 3 hr at room temperature and unchanged starting material was extracted with two 100-ml portions of diethyl ether. A solution of 54 g (0.66 mole) of dimethylamine hydrochloride in 67 ml of 30% aqueous formaldehyde was added dropwise with stirring into the aqueous phase obtained above. After allowing the reaction mixture to stand for 4 days at room temperature, it was acidified to pH 3 with 5 *N* hydrochloric acid and was evaporated to dryness *in vacuo*.

The resulting viscous oil, which contained sodium chloride, was dissolved in 800 ml of dry methanol. After removing the salt by filtration, dry hydrogen chloride gas was passed in and the solution was boiled for 16 hr and evaporated to dryness, and 300 ml of benzene was added and then distilled from the residue. The resulting material was boiled in 500 ml of dry methanol containing 1% hydrogen chloride for 8 hr, and after evaporation of the solvent 140 g of viscous, oily residue was dissolved in 200 ml of water (pH 3–4) and extracted three times with 50-ml portions of ether. The ethereal solution was dried over magnesium sulfate and evaporated to dryness and the residue (34 g) was distilled *in vacuo* yielding 20 g (21%) of product IIIg: bp 70–72° (2 mm), $n^{25}D$ 1.4500 [lit.[16] bp 77–81° (3 mm), $n^{20}D$ 1.4510]; $\lambda_{max}^{EtOH}$ 219 mμ (log ε 3.85); $\nu_{max}$ 1680 (CO), 1630 $cm^{-1}$ (C=C). The **dinitrophenylhydrazone** derivative had mp 123–124°.

*Anal.* Calcd for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.25; H, 4.91; N, 16.57.

The above aqueous solution, which was extracted with ether, was cooled and made alkaline with 2 *N* NaOH solution (pH 8.5–9) and extracted immediately with five 200-ml portions of ether. The combined extracts were dried and evaporated to dryness. The obtained oil (45 g) was mixed with 15 ml of dry methanol and 25 ml (0.4 mole) of methyl iodide and allowed to stand overnight. The precipitated crystals were collected by suction and washed with a small amount of absolute ether giving 60 g (30%) of product IXa: mp 110°, which rose to 118–119° after recrystallization from methanol–ether; $\nu_{max}^{KBr}$ 1730 ($COOCH_3$), 1710 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{11}H_{22}INO_3$: C, 38.48; H, 6.16; N, 4.08. Found: C, 38.24; H, 6.11; N, 3.85.

The above salt IXa (35 g, 0.102 mole) was dissolved in 25 ml of water with gentle warming and poured into a separatory funnel. After it was allowed to cool, 50 ml of ether was added and a solution of 4.1 g (0.102 mole) of sodium hydroxide in 6 ml of water was added dropwise over a period of 5 min. The solution was extracted every 15 min, with five 100-ml portions of ether. The combined extracts were dried and evaporated to dryness giving 13.4 g (87%) of product, which was identical with compound IIIg obtained above.

**2-Methylenelevulinic Acid Methyl Ester (IIIf) and 2-Dimethylaminomethyllevulinic Acid Methyl Ester Methyl Iodide (IXb).**[17]—Acetylsuccinic acid diethyl ester was treated according to the procedure described for compound IIIg yielding ketone IIIf (69%), which is an oil: bp 95–100° (14 mm), $n^{25}D$ 1.4330. **The dinitrophenylhydrazone** derivative had mp 130°

*Anal.* Calcd for $C_{13}H_{14}N_4O_6$: C, 48.13; H, 4.37; N, 17.07. Found: C, 48.23; H, 4.04; N, 17.34.

Quaternization with methyl iodide of the Mannich base produced, in addition to ketone ester IIIf, salt IXb, mp 143°.

*Anal.* Calcd for $C_{10}H_{20}INO_3$: C, 36.47; H, 6.12; N, 4.25. Found: C, 36.20; H, 6.08; N, 4.01.

Hofmann degradation of the methyl iodide IXb also yielded the derivative IIIf.

**9-Acetyl-9-ethyl-5,6,7,8,9,9a,15,16,17,17a-decahydropyrimido[2.1-*a*:4,3-*a*]di-β-carboline (IVb).** **A.**—Five milliliters (51 mmoles) of unsaturated ketone IIIb was added to a solution of 2.75 g (16 mmole) of base IIa in 30 ml of ethanol and allowed to stand at room temperature for 4 days. The precipitated crystals were collected by suction giving 2.70 g (78%) of derivative IVb, mp 205–207°. The compound is slightly soluble in ethanol. After recrystallization from dioxane–water the melting point rose to 208°; $\lambda_{max}^{EtOH}$ 282 mμ (log ε 4.165), 290 mμ (log ε 4.097); $\nu_{max}^{KBr}$ 1692 (CO), 3410 $cm^{-1}$ (shoulder at 3445 $cm^{-1}$) (NH). The compound showed nmr peaks (in $CDCl_3$) at δ 0.42 (methyl protons, triplet), 2.18 (acetyl group protons), 4.43 (C-9a proton), 4.71 (C-17a proton), 8.0 and 8.68 (protons of NH group). Molecular weight (mass spectrum) was 438 (calcd 438).

*Anal.* Calcd for $C_{28}H_{30}N_4O$: C, 76.68; H, 6.90; N, 12.78. Found: C, 76.48; H, 7.04; N, 12.63.

On evaporating the mother liquor to dryness and recrystallization of the residue from ethanol, 0.2 g of compound Ib (see below) was isolated.

**B.**—Compound IVb could be obtained if the reactants were warmed and allowed to stand at room temperature in DMF or without solvent. Boiling in benzene, ethyl acetate, or dioxane resulted in the same product.

The base IVb dissolves in alcoholic hydrochloric acid giving a yellow color. After 1 hr the hygroscopic salt VIII (R = $C_2H_5$, X = Cl) can be precipitated from the solution by addition of ether. Some of the salt (0.49 g) was dissolved in 10 ml of hot water, the pH was adjusted to 7 with aqueous ammonia, and the calculated amount of perchloric acid was added dropwise. The precipitated oil crystallized after addition of a small amount of alcohol, yielding 0.45 g (87%) of VIII (R = $C_2H_5$, X = $ClO_4$). It crystallized from ethanol in the form of yellow needles: mp 148–150°; $\lambda_{max}^{EtOH}$ 364 mμ (log ε 3.729), 290 (3.761), 280 (3.821); $\nu_{max}^{KBr}$ 3345 (NH), 1700 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{17}H_{21}N_2O \cdot ClO_4$: C, 55.35; H, 5.73; Cl, 9.62; N, 7.59. Found: C, 55.16; H, 5.66; Cl, 10.22; N, 7.57.

One-tenth of a gram of salt VIII (R = $C_2H_5$, X = $ClO_4$) was dissolved in 20 ml of water with gentle warming and after cooling, it was made alkaline to pH 9 with 5% sodium carbonate solution, thus precipitating 0.08 g of pseudo-base VIb. Its melting point was 97–107°. The compound could not be made analytically pure through repeated recrystallizations.

A solution of 0.3 g of pseudo-base VIb in 20 ml of methanol was hydrogenated in the presence of 0.5 g of 8% Pd–C. The calculated amount of hydrogen was absorbed within 15 min.

(11) R. N. Gupta and J. D. Spenser, *Can. J. Chem.* **40**, 2049 (1962).

(12) C. Szántay, L. Töke, and K. Honty, *Tetrahedron Letters*, 1665 (1965).

(13) C. Mannich and W. Hot, *Arch. Pharm.*, **265**, 593 (1927).

(14) C. Szántay, L. Töke, B. Bárczai, M. Kalaus, and G. Kalaus, *Periodica Polytech.*, **9**, 231 (1965).

(15) (a) H. Kappeler, D. Staufacher, and H. Schinz, *Helv. Chim. Acta*, **37**, 957 (1954); (b) F. Korte and H. Hachleidt, *Chem. Ber.*, **88**, 1679 (1955).

(16) I. N. Nazarov and Sz. I. Zavljanov, *Izv. Akad. Nauk SSSR, Otd. Khim.. Nauk*, 300 (1952).

(17) In collaboration with Mrs. Éva Szentirmay.

The solution was worked up in the usual manner and the product was fractionally recrystallized from ethanol giving 0.05 g of product Ib. In addition 0.1 g (35%) of tetrahydro-β-carboline derivative (VIa) was obtained in the form of white needles: mp 141°; $\lambda_{max}^{EtOH}$ 280 mμ (log ε 3.776), 290 mμ (log ε 3.712); $\nu_{max}^{KBr}$ 3300 (NH), 1705 cm$^{-1}$ (CO).

*Anal.* Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.31. Found: C, 75.60; H, 8.00; N, 10.81.

One-tenth of a gram of salt VIII (R = $C_2H_5$, X = Cl) was dissolved in 10 ml of ethanol together with 1 equiv of IIa. The solution was made alkaline by adding 1 equiv of sodium ethoxide. After standing at room temperature for 5 hr the solution was concentrated to half-volume *in vacuo*, the precipitation was filtered and extracted with warm dioxane. From the solvent the compound IVb (50 mg) crystallized.

The following compounds with analogous structure were obtained according to the procedure described for IVb (A).

Compound IVa was obtained in 34% yield: mp 218–219° (from dioxane–water); $\lambda_{max}^{EtOH}$ 282 mμ (log ε 4.342), 290 mμ (log ε 4.272); $\nu_{max}^{KBr}$ 1698 (CO), 3415 cm$^{-1}$ (shoulder at 3440 cm$^{-1}$) (NH). The compound showed nmr peaks (in deuteriopyridine) at 1.33 (singlet, methyl protons), 2.02 (acetyl group protons), 4.47 and 4.68 (angular protons), 8.40 (protons of indole NH). Molecular weight (mass spectrum) was 424, calcd 424.

*Anal.* Calcd for $C_{27}H_{28}N_4O$: C, 76.38; H, 6.65; N, 13.20. Found: C, 76.25; H, 6.53; N, 13.12.

Compound IVc was obtained in 52.8% yield: mp 197–198° (from dioxane–water); $\lambda_{max}^{MeOH}$ 282 mμ (log ε 4.103), 290 mμ (log ε 4.053); $\nu_{max}^{KBr}$ 1709 (CO), 3365 and 3420 cm$^{-1}$ (NH). Nmr peaks (in $CDCl_3$) were located at 0.59 (methyl protons), 2.12 (acetyl group protons), 4.25 and 4.28 (angular protons), 8.06 and 8.60 (protons of indole NH). Molecular weight was (mass spectrum) 452, calcd 452.

*Anal.* Calcd for $C_{29}H_{32}N_4O$: C, 76.96; H, 7.13; N, 12.38. Found: C, 76.83; H, 7.12; N, 12.27.

The 2-*n*-propylbuten-1-one-3, necessary for synthesis of IVc, was prepared, according to the procedure previously described,[5] in 50% yield: bp 140–143° (748 mm); $\nu_{max}$ 1624 (C=C), 1678 cm$^{-1}$ (CO conjugated).

Compounds IVd was obtained in 41% yield: mp 185–186° (from dioxane–water); $\lambda_{max}^{MeOH}$ 282 mμ (log ε 4.170), 290 (log ε 4.100); $\nu_{max}^{KBr}$ 1710 (CO), 1742 ($COOCH_3$), 3360 and 3430 cm$^{-1}$ (NH). Nmr peaks (in deuteriopyridine) were located at δ 2.25 (acetyl group protons), 2.83 (protons of $OCH_3$ group), 4.53 and 4.73 (angular protons), 8.33 protons of indole NH).

*Anal.* Calcd for $C_{29}H_{30}N_4O_3$: C, 72.18; H, 6.27; N, 11.61. Found: C, 71.99; H, 6.37; N, 11.66.

Compound IVe was obtained in 46% yield: mp 184–185° (from dioxane–water); $\lambda_{max}^{CHCl_3}$ 282 mμ (log ε 4.170), 290 mμ (log ε 4.079); $\nu_{max}^{KBr}$ 1695 (CO), 1730 ($COOCH_3$), 3370 and 3440 cm$^{-1}$ (NH). Nmr peaks (in $CDCl_3$) were located at δ 2.12 (acetyl group protons), 3.29 (methoxyl protons), 4.29 and 4.60 (angular protons), 7.96 and 8.56 (protons of indole NH). Molecular weight (mass spectrum) was 496, calcd 496, and 472 (vapor pressure osmometer in $CHCl_3$ at 37°).

*Anal.* Calcd. for $C_{30}H_{32}N_4O_3$: C, 72.55; H, 6.50; N, 11.28. Found: C, 72.41; H, 6.59; N, 11.19.

**Hydrogenolysis of IVb.**—One gram of IVb was dissolved in 60 ml of ethanol containing HCl and was hydrogenated in the presence of 10% Pd–C. The calculated amount of hydrogen was absorbed within 3 hr. The mixture was filtered and made alkaline, (pH 9) by ammonium hydroxide solution and the precipitated material was filtered. The residue was washed with water and recrystallized from ethanol yielding 0.31 g (50.8%) of VIa, identical with the compound obtained from VIb as described above.

More ammonium hydroxide solution was added to the mother liquor (pH 11) and the precipitated product was filtered. After recrystallization from ethanol 0.36 g (92.2%) of 1,2,3,4-tetrahydro-β-carboline was obtained, mp 207–208°.

Compound VIa was also prepared by dissolving 1 g of 1,2,3,4-tetrahydro-β-carboline in 50 ml of acetone, and adding 2 ml of 2-ethyl-buten-1-one-3. After being allowed to stand at room temperature for 3 days the solution was evaporated to dryness *in vacuo*. The residue was extracted by 120 ml of 3 *N* hydrochloric acid. The acid solution was made alkaline (pH with 9) with sodium hydroxide solution and extracted with 150 ml of benzene. After evaporation of the solvent and recrystallization of the residue from ethanol, 0.6 g (38.3%) of VIa was obtained, mp 141–142°.

**2-Oxo-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (Ib). A.**—The base, liberated from 2 g (11.7 mmoles) of its perchlorate (IIa), was dissolved in 10 ml of ethanol and to the warm solution 4 ml (41 mmoles) of ketone IIIb and a catalytic amount of ethanol, saturated with HCl, was added. The solution was boiled for 6 hr. After the solution was allowed to stand at room temperature overnight, the precipitated crystals (0.92 g) were collected and washed with ethanol. After concentration of the mother liquor an additional 0.3 g of product was obtained, yielding 1.22 g (39%) of white needles, mp 208°, after recrystallization from ethanol: $\lambda_{max}^{dioxane}$ 282 mμ (log ε 3.983), 290 mμ (log ε 3.916); $\nu_{max}^{KBr}$ 3356 (NH), 1708 cm$^{-1}$ (CO). The compound shows nmr peaks (in $CDCl_3$) at δ 0.96 (methyl protons) 3.57 (quartet), 8.1 (proton of indole NH). Molecular weight (by cyroscopic method in dioxane solution) was 270, calcd 268.

*Anal.* Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N 10.44. Found: C, 76.17; H, 7.24; N, 10.58.

Ketone Ib was obtained in a similar yield if the reaction was carried out using the crude 3,4-dihydro-β-carboline obtained from N-formyltryptamine.[14]

**B.**—A solution of 0.4 g (1.5 mmoles) of ketone IVb in 7 ml of 2 *N* hydrochloric acid was warmed on a steam bath for 1 hr. The yellow solution while warm was made alkaline with aqueous ammonium hydroxide. The precipitated crude product (0.4 g) was recrystallized from ethanol yielding 0.18 g (45%) of ketone Ib.

**C.**—A solution of 0.1 g of the pseudo-base VIb in 5 ml of ethanol was allowed to stand at room temperature for 1 day yielding 0.04 g (42%) of crystals of compound Ib.

According to procedure A described for compound Ib the following analogous products were obtained.

Compound Ia was obtained in 50% yield: mp 213–214° (from ethanol) (lit.[18] mp 209–211°); $\lambda_{max}^{EtOH}$ 290 mμ (log ε 3.771), 282 mμ (log ε 3.848); $\nu_{max}^{KBr}$ 3365 (NH), 1715 cm$^{-1}$ (CO). Nmr peaks (in deuteriopyridine) were located at δ 0.96 (doublet, $J$ = 6 cps, protons of the methyl group), 3.51 (quartet, $J$ = 10 cps, angular proton).

*Anal.* Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.87; H, 7.15; N, 10.98.

Compound Ic was obtained in 36% yield: mp 203–204° (from ethanol); $\lambda_{max}^{MeOH}$ 290 mμ (log ε 3.777), 282 mμ (log ε 3.842); $\nu_{max}^{KBr}$ 3360 (NH), 1712 cm$^{-1}$ (CO). Nmr peaks (in deuteriopyridine) were located at δ 0.82 (triplet, protons of the methyl group), 1.19 (multiplet, protons of the methylene group, adjacent to methyl group), 3.60 (quartet, $J$ = 10 cps, angular proton).

*Anal.* Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.42; H, 7.92; N, 9.85.

Compound Id was obtained in 46% yield: mp 172–173° (from ethanol); $\lambda_{max}^{EtOH}$ 290 mμ (log ε 3.789), 282 mμ (log ε 3.857); $\nu_{max}^{KBr}$ 3370 (NH), 1720 cm$^{-1}$ (CO).

*Anal.* Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.14; H, 7.97; N, 9.51.

Compound Ie was obtained in 93.6% yield: mp 227–228° (from ethanol); $\lambda_{max}^{EtOH}$ 290 mμ (log ε 3.787), 282 mμ (log ε 3.844); $\nu_{max}^{KBr}$ 3330 (NH), 1710 cm$^{-1}$ (CO).

*Anal.* Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 97.96; H, 6.86; N, 8.65.

If the components were treated as described for compound IVb, the products Id and Ie were obtained exclusively.

**2-Oxo-3-(β-methoxycarbonylethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (Ig). A.**—A solution of 8.8 g (52 mmoles) of the crude base IIa and 9 ml (57 mmoles) of the unsaturated ester IIIg in 90 ml of methanol was boiled for 16 hr. After the reaction mixture was allowed to stand overnight, the crystals were collected and washed with 3 ml of acetone and then with 3 ml of methanol yielding 6.4 g of material, mp 192°. After concentration of mother liquor an additional 0.8 g of product was obtained, yielding 7.2 g (41%) of ester Ig. Recrystallization from DMF–water and then dioxane–water afforded white needles: the melting point rose to 209–211°; $\lambda_{max}^{dioxane}$ 282 mμ (log ε 3.747), 290 mμ (log ε 3.666); $\nu_{max}^{KBr}$ 3380 (NH), 1722 ($COOCH_3$), 1710 cm$^{-1}$ (CO). Nmr peaks (in deuteriopyridine) were located at δ 3.59 (protons of $OCH_3$ group). Molecular weight (by cyroscopic method, in dioxane) was 330, calcd 326.

*Anal.* Calcd for $C_{19}H_{22}N_2O_3$: C, 69.61; H, 6.79; N, 8.58. Found: C, 69.83; H, 6.54; N, 8.61.

**B.**—A solution of 13.0 g (76 mmoles) of crude base IIa and 22 g (64 mmoles) of salt IXa in 150 ml of methanol was boiled

(18) U. S. Patent 2,908,686 (1961); *Chem. Abstr.*, **55**, 3622 (1961).

for 1 hr, and kept overnight at room temperature. The precipitated crystals were collected by suction and washed with methanol, water, and methanol again yielding 13 g (62%) of product, mp 205°, which was identical with the product obtained according to procedure A.

**2-Oxo-3-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (If).**—Five-tenths of a gram of compound IVd was dissolved in 10 ml of dry methanol to which was added 5 ml of methanol saturated with hydrogen chloride. After 30 min the yellow-green crystals were collected and dissolved in aqueous methanol. The solution was made alkaline to pH 8 with sodium carbonate solution giving 0.25 g (50%) of product, mp 212°. The melting point rose to 216° after recrystallization from methanol–water; $\lambda_{max}^{MeOH}$ 282 mμ (log ε 3.844), 290 mμ (log ε 3.772); $\nu_{max}^{KBr}$ 3360 (NH), 1755 ($COOCH_3$), 1710 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.20; H, 6.45; N, 8.96. Found: C, 69.20; H, 6.47; N, 9.16.

**2-Oxo-3-ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (Ih).**—To a solution of 1.3 g (33.3 mg-atoms) of metallic potassium in 50 ml of liquid ammonia a trace of iron(III) nitrate and 2.2 g (12.9 mmoles) of base IIa were added. After 10-min stirring of the reaction mixture, 70 ml of dry ether was added dropwise and boiled for 30 min. The mixture was cooled to 18° and 1.83 g (13 mmoles) of methyliodide was added and boiled for 4 hr. After being allowed to stand at room temperature overnight, the solution was filtered and the ether was distilled off. The yellow, oily residue (1.40 g) was recrystallized from benzene–petroleum ether yielding 0.7 g (29.5%) of base IIb. The melting point (153–154°) was unchanged after recrystallization from dioxane–water.

*Anal.* Calcd for $C_{12}H_{12}N_2$: C, 78.22; H, 6.57; N, 15.19. Found: C, 78.05; H, 6.42; N, 15.20.

The expected Ih was obtained in 46.1% yield when the reaction between base IIb and ketone IIIb was carried out as described in A for compound Ig: mp 184–185° (from ethanol), $\lambda_{max}^{dioxane}$ 281 mμ (log ε 3.495), $\nu_{max}^{KBr}$ 1708 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{18}H_{22}N_2O$: C, 76.85; H, 7.86; N, 9.93. Found: C, 76.71; H, 7.79; N, 10.11.

The quinolizine derivative Ih was obtained as well, if the components were treated by the method described for IVb, but the yield decreases to 10%.

**The Reaction of Base IIa with Acrylic Acid Ester and Acrylonitrile. A.**—To a solution of 0.3 g (1.76 mmoles) of base IIa in ethanol 0.5 g (5 mmoles) of ethyl acrylate was added and the mixture was allowed to stand overnight at room temperature yielding 0.37 g (79%) of product Xa: mp 182° dec after recrystallization from ethyl acetate; $\lambda_{max}^{dioxane}$ 282 mμ (log ε 4.213); $\lambda_{max}^{EtOH}$ 282 mμ (log ε 4.238), 290 mμ (log ε 4.172); $\nu_{max}^{KBr}$ 1723 $cm^{-1}$ ($COOC_2H_5$).

*Anal.* Calcd for $C_{32}H_{38}N_4O_4$: C, 71.09; H, 6.71; N, 10.37. Found: C, 70.97; H, 6.59; N, 10.38.

A catalytic hydrogenation of the product in DMF in the presence of Pd–C afforded **2-(β-ethoxycarbonylethyl)-1,2,3,4-tetrahydro-β-carboline (XI)** in almost quantitative yield. It crystallized from ethanol in the form of white needles: mp 125–126°; $\nu_{max}^{KBr}$ 1705 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C, 70.57; H, 7.40; N, 10.29. Found: C, 70.20; H, 7.06; N, 10.39.

**B.**—The reaction between 0.3 g (1.76 mmoles) of base IIa and 0.5 g (9 mmoles) of acrylonitrile was carried out in the same manner as described above giving the product Xb in 81.5% yield. For purification it was heated in 15 parts of DMF to 120°; the crystals were collected while the solution was still warm and were washed with ethanol. The white, crystalline material (mp 192°) is only very slightly soluble in organic solvents: $\nu_{max}^{KBr}$ 2245 $cm^{-1}$ (CN).

*Anal.* Calcd for $C_{23}H_{26}N_6$: C, 75.29; H, 5.86; N, 18.83. Found: C, 75.42; H, 5.79; N, 18.62.

**Measurement of the Reaction Rate of the Ring Splitting of Compounds IV.**—About 2 mg of the appropriate compound IV, which was to be investigated, was weighed into a 100-ml volumetric flask and dissolved in 0.15 ml of dimethyl sulfoxide. The flask was filled to the mark with 0.001 *N* hydrochloric acid and placed in a thermostated bath set at appropriate temperature. At initial intervals of 1 min, later in 5-min intervals, a sample was removed and the extinction value was measured at 362 mμ with Unicam-SP 700 spectrophotometer. At this wavelength the immonium salts of type VIII absorb strongly, while starting materials do not absorb.

The rate measurements were taken at +10 ± 0.01° and +25 ± 0.01°. As expected, the reaction was kinetically first order. In view of the fact that the transition-state parameters ($\Delta H^*$ and $\Delta S^*$) were calculated from the reaction rate constant determined only at two different temperatures, the numerical values must be regarded only as approximate.

Infrared absorption spectra were determined on a Perkin-Elmer Model 221G spectrophotometer; the ultraviolet spectra were obtained using a Unicam-SP 700 spectrophotometer; the nmr spectra were determined on a Varian A-60 spectrometer with tetramethylsilane as an internal standard; and the mass spectra were measured on a A.E.I. Type MS9 mass spectrometer.

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