CARBOLINES

I. 1, 4-Disubstituted β-Carbolines*

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4-Substituted 3, 4-dihydro-β-carbolines (X–XVI) were obtained by the Beckman rearrangement of oximes of β-(indolyl-3')ketones (I–IV, IX) under the action of phosphorus pentachloride in nitrobenzene. 3, 4-Dihydro-β-carbolines were converted into β-carbolines (XV–XVII) on heating with Brown's palladium catalyst in ethylene glycol. Oximes containing the aryl group react on treatment with p-toluene sulfochloride in pyridine with the formation of the arilides of β-(indolyl-3')propionic acids.

There is a very limited information about the synthesis and properties of the 4-substituted β-carbolines. The formation of a number of derivatives of tetrahydro-β-carboline with a methyl group in position 4 has recently been described [1, 2]. More complex compounds of the series under examination are also known such as the 6-alkyl deserpidines [3–5], the natural alkaloids from Carex brevicollis [6, 7],and salts of 13H-indolo[2, 3–a]quinolizinium [8]. As certain of these compounds are physiologically active substances, it was of interest to synthesize a series of new compounds of this type.

Recently in this laboratory a convenient method has been elaborated for preparing 3-substituted β-carbolines by the Beckman rearrangement of the oxines of β-(indolyl-3')ketones [9, 10]. Now an attempt has been made to use this method for the synthesis of 4-substituted harmans. With this object a study was made of the rearrangement of 4-substituted oximes of β-(indolyl-3')ketones, a great number of which have been previously described [11, 12]. It was found that these oximes sharply differ from their α-substituted analogous according to their reaction capacity. On treatment with tetraacetyldiborate in nitromethane [10] they give rise only to unstable complexes which are very readily hydrolyzed with the regeneration of the original compounds. The use of other methods indicated in previous studies [9, 10], and also other well-known methods of conducting the Beckman rearrangement, were also found to be ineffective. However it was found that the reaction proceeds in the desired direction if one reacts the oximes under investigation with phosphorus pentachloride in a polar homogeneous medium. Better results were obtained by treating the oximes at increased temperature with an excess of phosphorus pentachloride in a solution of nitrobenzene. By this means moderate yields of 3, 4-dihydro-β-carbolines (X–XVI) were synthesized which were isolated and characterized in the form of hydrochlorides or picrates. Their structure was confirmed by IR and UV spectroscopy.

The oxime of compound IV, containing the phenyl group in the β-position, did not give rise to individual products when it was treated by the above-mentioned method. From data obtained previously [9, 10] and results of the present study it was concluded that the effectiveness of the reaction under examination is dependent on the stability of the nonclassical cation (XXII), the formation of which has been postulated as one of the transitional states during the Beckman rearrangement [13]. The presence of the electron donor substitute R^3 in compound XXII raises the stability of this cation and the rearrangment proceeds readily. In the case of the oximes I–IV and IX this additional factor which stabilizes the positive charge is absent and the reaction is made more difficult. In compound IV the presence of the electron-acceptor phenyl group makes the conditions even more unfavorable, as a result of which the oxime IV is converted into 3, 4-dihydro-β-carboline (XIV) only on addition of dioxane, a solvent with a high solvating capacity. In this case apparently the stability of the cation increases on account of the solvation.

The oximes of the phenyl ketones (V, VI) did not form dihydro-β-carbolines during treatment with phosphorus pentachloride. However they were subjected to the Beckman rearrangement under the action of p-toluene sulfochloride in pyridine, forming anilides of substituted indolylpropionic acids (XVIII, XIX). On alkaline saponification the latter were cleaved into the respective acids and aniline. The yields in both stages were high and the reaction may be of preparative significance. It probably proceeds through a transitional state analogous to the phenonium ion, and must be

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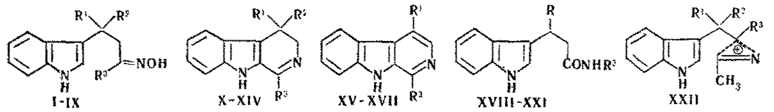
*For preliminary report, see [18].

accelerated by electron donor substitutes in the benzene nucleus [14]. With the object of increasing the yields of amides the p-tolyl- and p-methoxy phenyl ketones were synthesized by the interaction between indole and the corresponding chalcones in the presence of perchloric acid. The oximes of these ketones (**VII** and **VIII**) reacted more rapidly than the unsubstituted analog, although no increase in yield of the amides was observed.



Compound	R^1	R^2	R^3
I, X, XV	C_3H_7	H	CH_3
II, XI, XVI	$i\text{-}C_4H_9$	H	CH_3
III, XII	CH_3	CH_3	CH_3
IV, XIV, XVII	C_6H_5	H	CH_3
V, XVIII	CH_3	H	C_6H_5
VI, XIX	C_6H_5	H	C_6H_5
VII, XX	C_6H_5	H	$p\text{-}C_6H_4CH_3$
VIII, XXI	C_6H_5	H	$p\text{-}C_6H_4OCH_3$
IX, XIII	H	H	CH_3

The 3,4-Dihydro-β-carbolines (**X, XI,** and **XIV**) were converted into aromatic compounds (**XV–XVII**). Thus the hydrochlorides of the original compounds are not sufficiently stable at high temperatures, so that a mild method of dehydrogenation had to be used. Attempts to use chloranil or a previously described method [15] were not successful. In a number of publications, described in a previous article [16]. Brown described the preparation of active catalysts of hydrogenation by the reduction of salts of the platinum metals with sodium borohydryde. A palladium catalyst prepared according to the method of Brown was found to be very effective for dehydrogenation and by using this method it was possible to obtain high yields of β-carbolines(**XV–XVII**). The reaction was achieved by heating the hydrochlorides of compounds **X**, **XI**, and **XIV** in aqueous ethylene glycol with maleic acid and a catalyst prepared directly in the reaction vessel.

By preliminary pharmacological tests conducted by K. L. Matkovskii in the Institute of Medicine, Kishinev, it was established that β-carbolines (**XV–XVII**) depress the central nervous system.

EXPERIMENTAL

All melting points are not corrected and the majority of them are determined in Kofler's apparatus.

UV spectra were recorded in ethyl alcohol in an SF-4 apparatus, and the IR spectra were determined in the UR-10 apparatus.

1-Phenyl-3-(indolyl-3')-1-oxobutane. A 0.55 g quantity of 70% perchloric acid was added to a mixture of 5.5 g (0.047 mole) indole in 10 g (0.07 mole) ethylidene acetophenone at 0° C, the mixture was stirred until a homogeneous mixture was obtained and maintained for 7 hr at the same temperature. The solidified mass was dissolved in benzene, washed with a solution of soda, and dried with sodium sulfate. After removal of the solvent by distillation the precipitate was recrystallized from benzene. A 6.9 g quantity (56%) of the substance was obtained, mp 108–109° C. Found, %: C 82.0; H 6.4; N 5.5. Calculated for $C_{18}H_{17}NO$: %: C 81.2; H 6.5; N 5.3. IR spectrum, cm^{-1}. 3370 (NH), 1668 (C═O). Oxime (V), mp 137–139° C (from CCl_4). Found, %: C 77.8; H 6.6; N 10.0. Calculated for $C_{18}H_{18}N_2O$, %: C 77.7; H 6.5; N 10.0. IR spectrum, cm^{-1}: 3440 (NH), 3230 (OH), 1635 (C═N).

3-Phenyl-1-n-tolyl-3-(indolyl-3')-1-oxopropane. A 25-mg quantity of 70% perchloric acid was added to an alloy of 0.25 g (2.1 mM) indole and 0.71 g (3.3 mM) p-methylchalcone at 80° C, and the mixture was stirred for 30 min at the same temperature. A 2.5-ml volume of benzene was poured into the hot mixture and the resulting solution was shaken with a solution of sodium bicarbonate. The organic layer was maintained overnight at room temperature. The crystals which separated out were removed by filtration and recrystallized from benzene. A 0.4 g quantity (55%) of colorless crystals were obtained, mp 172° C. Found, %: C 84.9; H 6.1; N 4.1. Calculated for $C_{24}H_{21}NO$, %: C 84.9; H 6.2; N 4.1. IR spectrum, cm^{-1}; 3450 (NH), 1678 (C═O). Oxime (VII), mp 201–202° C (from ethanol). Found, %: C 81.3; H 6.5; N 7.9. Calculated for $C_{24}H_{22}N_2O$, %: C 81.3; H 6.3; N 7.9. IR spectrum, cm^{-1}: 3410 (NH), 3280, 3210(OH), 1610 (C═N).

3-Phenyl-1-(p-methoxyphenyl)-3-(indolyl-3')-1-oxopropane. This compound was obtained from indole and p-methoxychalcone with a yield of 70%; mp 179–180° C (from ethanol). Found, %: C 81.1; H 6.0; N 4.0. Calculated for $C_{24}H_{21}NO_2$, %: C 81.1; H 6.0; N 3.9. IR spectrum cm^{-1}: 3450 (NH), 1668 (C=O). Oxime (VIII), mp 172–173° C (from 2-propanol). Found, %: C 77.7; H 5.9; N 7.6. Calculated for $C_{24}H_{22}N_2O_2$, %: C 77.8; H 6.0; N 7.6. IR spectrum, cm^{-1}: 3430 (NH), 3310 (OH).

Hydrochloride of 1-methyl-4-propyl-3,4-dihydro-β-carboline (X). A 5.66-g quantity (0.023 mole) of compound I was sprinkled in small portions over the course of 2 min into a solution of 14.8 g (0.071 mole) of phosphorus pentachloride in 113 ml nitrobenzene, heated to 45–50° C with vigorous stirring, and the temperature spontaneously increased to 60–65° C. The reaction mixture was rapidly cooled, the excess phosphorus pentachloride was decomposed with pieces of ice, ether was added, and it was extracted with dil HCl. The aqueous phase was washed with organic solvents, made alkaline with ammonia, and extracted with ether. A solution of hydrogen chloride was poured into the dried extract, and the precipitated hydrochloride was separated and dissolved in boiling dichlorethane. When the dichlorethane was allowed to evaporate freely, yellow crystals were formed which were removed by filtration and carefully washed with dichlorethane. A 3.04-g (49%) quantity of the hydochloride of compound **X** was obtained, mp 203–204° C (from 2-propanol). Found, %: C 68.7; H 7.1; N 10.8. Calculated for $C_{15}H_{18}N_2 \cdot HCl$, %: C 68.6; H 7.3; N 10.7. IR spectrum, cm^{-1}: 3320 (NH), 1638 (C=N). UV spectrum, λ_{max}, nm (log ε), hydrochloride: 214 (4.36), 246 (4.14), 353 (4.47); base: 235 (4.31), 315 (4.29).

Hydrochloride of 1-methyl-4-isobutyl-3,4-dihydro-β-carboline (XI). A 0.22-g (0.85 mM) quantity of compound **II** in 2.2 ml nitrobenzene was added to 0.52 g (2.5 mM) of phosphorus pentachloride in 2.3 ml nitrobenzene at 100° C within 0.5 min, the mixture was stirred for a further 0.5 min and then treated as described for compound **X**. A 0.11-g (48%) quantity of yellow crystals of the hydrochloride of compound **XI** was obtained, mp 178–179° C (from dichlorethane). Found, %: C 69.5; H 7.8; N 10.1; Cl 12.6. Calculated for $C_{16}H_{20}N_2 \cdot HCl$, %: C 69.4; H 7.6; N 10.1; Cl 12.8. IR spectra, cm^{-1}: 3380 (NH), 1630 (C=N). UV spectrum, λ_{max}, nm (log ε): 246 (3.94), 352 (4.27).

Picrate of 1,4,4-trimethyl-3,4-dihydro-β-carboline (XII). An ethereal solution of the base was obtained in an analogous manner to compound **XI** from compound **III** at 70° C. The picrate was precipitated by the addition of a solution of picric acid in ether and it was recrystallized from propanol. Yield, 31%, mp 247° C. Found, %: C 54.7; H 4.3; N 15.8. Calculated for $C_{14}H_{16}N_2 \cdot C_6H_3N_3O_7$, %: C 54.4; H 4.3; N 15.9. IR spectrum, cm^{-1}; 3380 (NH), 1632 (C=N). Hydrochloride of compound **XII**, mp 217–219° C (from 2-propanol). UV spectrum, λ_{max}, nm (log ε): 246 (4.07), 351 (4.43).

Picrate of 1-methyl-3,4-dihydro-β-carboline (XIII). This compound was obtained in a similar manner to compound **XII** with a yield of 9–10%; mp 236° C (from acetone). A mixed sample with an authentic sample did not give a depression.

1-Methyl-4-propyl-β-carboline (XV). A 0.27 g quantity (7.2 mM) of sodium borohydride in 14 ml water was added with stirring to a solution of 0.51 g (2.4 mM) of $PdCl_2 \cdot 2H_2O$ in 45 ml water at 25° C in a stream of nitrogen. After 1–2 min the solution was acidified with HCl, and 1.32 g (11.4 mM) maleic acid in 10 ml water and 0.6 g (2.28 mM) of hydrochloride of compound **X** in 30 ml water were added. The apparatus was transferred to an oil bath connected to a reflux condenser and the water was removed, and 45 ml ethylene glycol was added gradually. After the temperature of the reaction mixture had reached 140° C, it was heated for a further 1.5 hr. The catalyst was then removed by filtration, the solution was dissolved in water, made alkaline with potash, and extracted with ether. After the solvent had been removed by distillation, the residue was recrystallized from trichlorethylene. A 0.48-g quantity (94%) of white crystals of compound **XV** was obtained; mp 197.5–198.5° C. Found, %: C 80.4; H 7.4; N 12.5. Calculated for $C_{15}H_{16}N_2$, %: C 80.3; H 7.2; N 12.5. IR spectrum, cm^{-1}: 3450(NH), 1650 (C=N). UV spectrum, λ_{max}, nm (log ε): 237 (4.71), 243 (4.73), 287 (4.24), 337 (3.85), 350 (3.89). Hydrochloride of compound **XV**, mp 223–224° C (from ethanol in a sealed capillary). IR spectrum, cm^{-1}: 3380 (NH), 2600 ($\equiv N^{+}H$), 1640 (C=N).

1-Methyl-4-isobutyl-β-carboline (XVI). This compound was obtained from compound **XI** in an analogous manner to compound **XV**. Yield, 67%. Mp 198–200° C (from trichlorethylene). Found, %: C 80.3; H 7.5 N 11.6. Calculated for C 80.6; H 7.6; N 11.8. IR spectrum, cm^{-1}: 3400 (NH), 1620 (C=N). UV spectrum, λ_{max}, nm (log ε): 244 (4.67), 285 (3.99), 335 (3.75), 350 (3.80). Hydrochloride of compound XVI, mp 235–236° C (from 2-propanol).

1-Methyl-4-phenyl-β-carboline (XVII). A 5.3-g (0.019 mole) quantity of compound **IV** in 53 ml absolute dioxane (increase of in temperature to 70° C) was added within 1 min with stirring to a solution of 11.75 g (0.056 mole) phosphorus pentachloride in 53 ml nitrobenzene heated to 50° C. The reaction mixture was rapidly cooled and treated as described during the preparation of compound **X**. A 1.15-g quantity of the crude hydrochloride of compound **XIV** was obtained. UV spectrum, λ_{max}, nm (log ε): 248 (4.16), 353 (4.39). This substance was added to the solution for dehydrogenation, obtained from 1.96 g (0.09 mM) $PdCl_2 \cdot 2H_2O$, 80 ml ethylene glycol, and 4.5 g (3.9 mM) maleic acid. The mixture was stirred in an atmosphere of nitrogen at 160° C for 3 hr. The product of the reaction after normal treatment was chromatographed on 50 g aluminum oxide of grade III activity. A 0.64-g (13%) quantity of colorless crystals XVII was washed with benzene: mp 226° C (from trichloethylene). Found, %: C 84.1; H 5.4; N 10.6. Calculated for $C_{18}H_{14}N_2$, %: C 83.7; H 5.5; N 10.8. Hydrochloride of compound **XVII**, mp 271–273° C (from 2-propanol, in a sealed capillary). Found, %: C 73.5; H 5.4; N 9.3; Cl 11.6. Calculated for $C_{18}H_{14}N_2$, %: C 73.3; H 5.1; N 9.5; Cl 12.0. UV spectrum, λ_{max}, nm (log ε): 225 (4.28), 259 (4.05), 305 (4.03), 375 (3.82). IR spectrum, cm^{-1}: 3450 (NH), 2730 ($\equiv N^+H$), 1640 (C=N).

Anilide of 3-phenyl-3-(indolyl-3')propionic acid (XIX). A 185-mg (0.97 mM) quantity of p-toluenesulfochloride was gradually added with stirring to a solution of 275 mg (0.8 mM) compound VI in 2.75 ml dry pyridine cooled with ice, and the mixture was maintained for 6 hr at 20° C. The solution was poured into 30 ml water, extracted with ethyl acetate, washed with dil HCl, water, and a soda solution. After drying the extract was evaporated to a volume of approximately 1 ml. On standing 206 mg (75%) of colorless crystals of compound **XIX** separated out; mp 193–195° C (from ethanol). Found, %: C 81.1; H 6.2; N 8.1. Calculated for $C_{23}H_{20}N_2O$, %: C 81.2; H 5.9; N 8.2. IR spectra, cm^{-1}: 3400 (NH-indole), 3290, 3070, 1645, 1300 (NH—CO).

The following substances were obtained in similar manner:

p-Toluidide of 3-phenyl-3-(indolyl-3')propionic acid (XX); Yield, 74%; mp 192–193° C (from ethanol. Found, %: C 81.6; H 6.4; N 7.8. Calculated for $C_{24}H_{22}N_2O$, %: C 81.3; H 6.3; N 7.9.

p-Methoxyanilide of 3-phenyl-3-(indolyl-3')propionic acid (XXI). Yield, 70%; mp 222–223° C (from ethanol) Found, %: C 78.0; H 6.0; N 7.6. Calculated for $C_{24}H_{22}N_2O_2$, %: C 77.8; H 6.0; N 7.6.

Anilide of 3-(indolyl-3')butyric acid (XVIII); Yield, 63%; mp 133–135° C (from chloroform). Found, %: C 77.4; H 6.5; N 10.2. Calculated for $C_{18}H_{18}N_2O$, %: C 77.7; H 6.5; N 10.1.

3-Phenyl-3-(indolyl-3')propionic acid. A mixture of 0.72 g (2.1 mM) of compound **XIX**, 2.33 g (42 mM) potassium hydroxide and 14.4 ml of glycol was heated for 1 hr at 185–190° C, and then poured into 70 ml water. Aniline was extracted with ether, and the aqueous layer was acidified with conc HCl and again extracted with ether. On evaporation of the second extract 0.48 g (86%) of a crystalline mass was obtained, mp 172–174° C (from benzene). IR spectrum, cm^{-1}: 3450 (NH), 2700–2600, 1710, 1690 (COOH). Methyl ester, mp 114–115° C (from propanol). Found, %: C 77.4; H 6.2; N 5.0. Calculated for $C_{18}H_{17}NO_2$, %: C 77.4; H 6.2; N 5.0. Sodium salt, mp 232–234° C (from 2-propanol).

3-(Indolyl-3')butyric acid. This compound was obtained in an analogous manner by saponification of compound XVIII, and isolated in the form of a complex with sym-trinitrobenzene with a yield of 52%; mp 136–137° C (from dichlorethane). According to data in the literature [17], mp 153° C. Found, %: C 51.7; H 3.8; N 13.5. Calculated for $C_{12}H_{13}NO_2 \cdot C_6H_3(NO_2)_3$, %: C 51.9; H 3.9; N 13.5. IR spectrum, cm^{-1}: 3500 (NH), 2700–2600, 1710 (COOH), 1550, 1350 (NO_2).

REFERENCES

1. J. I. De Graw, I. G. Kennedy, and W. A. Skinner, J. Med. Chem., 10, 127, 1967.
2. J. I. De Graw and W. A. Skinner, Can. J. Chem., 45, 63, 1967.
3. L. Velluz, G. Muller, and A. Allais, C. r., 247, 1747, 1958.
4. G. Muller, A. Allais, and L. Velluz, French patent no. 1344152, 1963; RZhkh, 1965, 14H235.
5. French patent, no. 1369323, 1366730, 1369956, 1964, RZhKh, 1H191, 193, 194, 1966.
6. P. A. Vember, I. V. Terent'eva, and G. V. Lazur'evskii, KhPS [Chemistry of Natural Compounds], 249, 1967.
7. P. A. Vember and I. V. Terent'eva, KhPS [Chemistry of Natural Compounds], 98, 1968.
8. C. K. Bradsher and E. F. Litzinger, J. Org. Chem., 29, 3584, 1964.
9. A. A. Semenov, I. V. Terent'eva, and E. P. Styngach, KhGS [Chemistry of Heterocyclic Compounds], collection 1, 38, 1967.
10. A. A. Semenov, KhGS [Chemistry of Heterocyclic Compounds], collection 1, 44, 1967.
11. A. A. Semenov, E. P. Styngach, and G. M. Kuperman, KhGS [Chemistry of Natural Compounds], 878, 1968.

12. J. Szmuszkowicz, J. Am. Chem. Soc., **79**, 2819, 1957.
13. R. T. Conley and R. E. Novak, J. Org. Chem., **27**, 3196, 1962.
14. L. G. Donaruma and V. Z. Khel'dt, Org. reaktsii, **11**, 14, Moscow, 1965.
15. E. Wenkert and D. K. Rovchaundhuri, J. Am. Chem. Soc., **80**, 1613, 1958.
16. H. C. Brown, Tetrah., **22**, Suppl. 8, 149, 1966.
17. L. E. Weller and T. L. Rebstock, J. Am. Chem. Soc., **74**, 2690, 1952.
18. K. I. Kuchkova and A. A. Semenov, KhGS [Chemistry of Nutural Compounds], 1136, 1967.

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