mixture was stirred for one hour at room temperature. The crystalline product was filtered and washed with water. After drying, it weighed 20 g. (90% yield). Recrystallization of the crude product from alcohol–benzene and from benzene gave 17 g., m.p. 256–259°.

Anal. Calcd. for $C_{12}H_{18}N_6$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.55; H, 7.19; N, 33.80.

Compound II did not react detectably with sodium thiosulfate under conditions which give rapid, quantitative conversion of 1-aziridinyl-*s*-triazines to the Bunte salts.[2] This test was complicated by the insolubility of II in the reagent, but the conclusion nevertheless seems warranted that the azetidine derivative has a much lower order of reactivity than triethylenemelamine. Compound II could be titrated to a sharp end-point with 0.5 *N* hydrochloric acid thus showing its distinction from triethylenemelamine in reactivity to acids.[3]

Attempted Preparation of N-Cyanoazetidine.—Reaction of trimethylene dibromide with equivalent amounts of cyanamide and sodium hydroxide in 25% aqueous ethanol was 90% complete in 3 hours at 70–75° as judged by the disappearance of the alkali. However, only 15–20% of the expected weight of product could be extracted from the reaction mixture with benzene. Only a small portion of this was distillable below 100° at 6 mm. Thus, the yield of N-cyanoazetidine was negligible.

When this reaction was tried in substantially dry ethanol, slightly better results obtained. A mixture of 39.5 g. (0.44 mole) of sodium acid cyanamide,[15] 89.8 g. (0.44 mole) of trimethylene dibromide and 17.8 g. (0.44 mole) of sodium hydroxide in 200 cc. of ethanol reacted exothermically. After 30 minutes at 50° and one hour at 78° the reaction mixture was filtered. The solution was concentrated, and the residue was distilled at low pressure. Approximately 8 g. of material boiling at 75–85° at 3 mm. was obtained. This had a neutral equivalent of 179 (basic) which corresponded to a mixture of about 29% N-cyanoazetidine and 71% O-ethyl-N,N-trimethyleneurea. This identification was supported by infrared absorption spectra. On this basis, the total yield of these compounds was only 16%.

(15) Commercial 72% sodium acid cyanamide was used. This contained a substantial amount of sodium carbonate.

STAMFORD, CONN.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

The Relative Basicities of α-, β- and γ-Carboline Anhydronium Bases

BY ALLAN P. GRAY

RECEIVED JUNE 2, 1955

Dissociation constants have been determined for simple carboline anhydronium bases. The observed order of base strength ($\beta > \gamma > \alpha$) may be rationalized qualitatively in terms of resonance theory.

The early, pioneering researches of Robinson and his co-workers did much to clarify the then obscure properties of the carboline anhydronium bases.[1,2] Largely as a result of the finding of this system in a number of naturally occurring alkaloids, β-carboline anhydronium bases have lately been subjected to intensive study,[3] whereas their α- and γ-analogs have been relatively neglected.[4]

In connection with an attempt to correlate the chemical with biological properties of some bis-carboline salts,[5] we had occasion to determine the approximate dissociation constant of α-carboline methiodide and noted the pK_a value to be markedly lower than values that had been reported for certain β-carboline derivatives.[6] The β-carboline salts for which data are available[6] are all alkaloids of quite complex structure, and apparently no measurements have been reported for other carboline systems. It thus appeared of interest to determine and compare the dissociation constants of simple α-, β- and, also, γ-carboline anhydronium bases. Since the ionization of acids and bases is a thermodynamically controlled equilibrium process, such data would permit insight into the relative stabilities of these anhydronium bases and their corresponding conjugate acids.

α-Carboline methiodide, norharman (β-carboline) methobromide and harman methobromide were at hand from the earlier study.[5] γ-Carboline was synthesized by the method of Robinson and Thornley[4] with the exception that the required intermediate, 4-chloropyridine, was obtained from the reaction of phosphorus oxychloride with pyridine N-oxide.[7] The dissociation constants were determined by potentiometric titration (Beckman, glass electrode *p*H meter) with 0.1 *N* sodium hydroxide of carbon dioxide-free, 60% ethanol solutions of the carboline methohalide salts. The alcoholic solvent was used owing to the tendency of the β-carboline derivatives (but not the α- or γ-isomers) to precipitate during the course of titration in water. The *p*H at 50% neutralization was taken without refinement to represent the pK_a value. The point of 50% neutralization was readily determinable in the case of α-carboline methiodide which afforded a titration curve with a sharp inflection at the end-point, but had to be calculated for the β- and γ-isomers, the curves of which showed no such clear breaks.[8] The results listed in Table I

(1) J. W. Armit and R. Robinson, *J. Chem. Soc.*, **127**, 1604 (1925), adopted the general term *anhydronium base* for "the anhydro derivatives of aromatic onium hydroxides," important resonance forms of which are (a) aromatic with complete separation of charge and (b) quinonoid.

(2) *Chemical Abstracts* nomenclature is 9-pyrid-2,3b-indole for α-carboline, 9-pyrid-3,4b-indole for β-carboline and 5-pyrid-4,3b-indole for γ-carboline. The trivial names are used for convenience.

(3) *Cf.* B. Witkop, THIS JOURNAL, **75**, 3361 (1953); and H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951), for recent investigations of these interesting substances and for an introduction to the literature.

(4) *Cf.* R. H. Freak and R. Robinson, *J. Chem. Soc.*, 2013 (1938), for studies on α-carboline; R. Robinson and S. Thornley, *ibid.*, **125**, 2169 (1924), for γ-carboline.

(5) A. P. Gray, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **76**, 2792 (1954).

(6) V. Prelog, *Helv. Chim. Acta*, **31**, 558 (1948), reported a pK_a of 10.6 for sempervirine. H. Schwarz and E. Schlittler[3] reported values of from 10.4–10.7 for serpentine, alstonine and two related alkaloid derivatives. Measurements were made in 40% methanol solution by titration of the salts with tetramethylammonium hydroxide.

(7) *Cf.* M. Murakami and E. Matsumura, *J. Chem. Soc. Japan*, **70**, 236 (1949), *C. A.*, **45**, 4698d (1951), T. Kato and M. Ohta, *J. Pharm. Soc. Japan*, **71**, 217 (1951), *C. A.*, **46**, 4541a (1952).

(8) Presumably, this is a result of the titration of extremely weak acids in dilute solution.

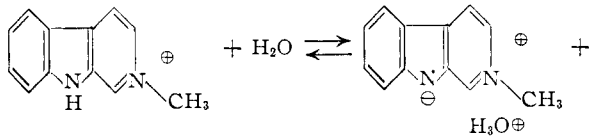
represent average values from several determinations for each salt.

TABLE I

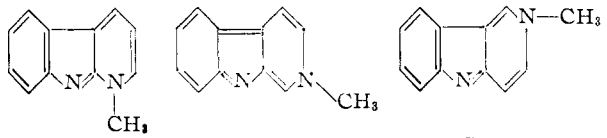
Anhydronium base	pK_a[a]
Py-N-Methyl-α-carboline	7.75
Py-N-Methylnorharman	11.11
Py-N-Methylharman	11.20
Py-N-Methyl-γ-carboline	10.54
1-Methyl-2-pyridonimine	12.20[b]
1-Methyl-4-pyridonimine	12.5[b]

[a] Measurements made on the corresponding salts at 25° in 60% ethanol solution. [b] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1461 (1952). These measurements were made in water.

The observed order of base strength is β- > γ- >> α-carboline anhydronium base. Despite the errors implicit in attempts to draw conclusions from pK_a data,[9] a qualitative evaluation of the results seems justified, particularly since measurements were made at similar concentrations of the salts in the same solvent system. The equilibrium involved may be expressed as (*e.g.*, in the case of the β-derivative)



Presumably, the greater basicity of the β-derivative, which of course implies a larger increase in free energy involved in removing a proton from the salt, can in large part be ascribed to a lower stabilization energy of the β-carboline anhydronium base. This is suggested by consideration of the relative contributions made by the quinonoid canonical forms (A, B and C) to the over-all stability of these bases.



Since B, which requires disruption of the symmetric resonance of the benzenoid ring, is a relatively high energy structure, the β-base would be expected to be energetically less favored than either of its analogs.

The low base strength of the α- as compared with the γ-derivative can be interpreted on the basis of two complimentary factors: (a) a much increased stability of the α-anhydronium base as a result of the juxtaposition of the oppositely charged centers; and (b) a reduced stability of the α-carboline salt owing to the inductive effect of the indole nitrogen attached to the same carbon as the positively charged pyridine nitrogen. Particularly intriguing in its possible implications is the fact that the γ-derivative is much closer in pK_a value to the β- ($\Delta\beta,\gamma$ = 0.6 pK_a unit) than to the α-isomer ($\Delta\gamma,\alpha$ = 2.8 pK_a units). This would seem to be most unusual. Of interest in this connection are the base strengths of what may be considered as the simplest analogs of the α- and γ-carboline anhydronium bases, the 1-methyl-2-, and -4-pyridonimines. That the carbolines are weaker bases than are the pyridonimines is thus unexceptional since they may be regarded as N-phenyl substituted pyridonimine derivatives. More pertinent is the fact that there is a much smaller difference in pK_a between the 2- and 4-pyridonimines than between the α- and γ-carboline anhydronium bases. In view of the extremely high base strengths of the pyridonimines, there is a possibility that this is partially due to some levelling effect of the solvent.[10] Nevertheless, it is worth noting that whereas the difference in base strength between β- and γ-carboline derivatives has been ascribed to differences in the quinonoid forms of the anhydronium bases, pK_a differences between α- and γ-carboline analogs and between 2- and 4-pyridonimines should primarily depend on contributions to stability by the aromatic, charge-separated structures. The fact that the pK_a of the 2-pyridonimine is close to that of the 4-isomer thus suggests, as would be expected (see also the reference in footnote *b*, Table I), that the structures of the pyridonimines are more closely approximated by the quinonoid rather than by the aromatic canonical forms. In contrast, the fact that the γ-carboline base is much closer in pK_a to the β- than to the α-analog may be taken as rather tenuous evidence indicating that the aromatic, charge-separated forms more nearly represent the properties of all three anhydronium bases. The high dipole moment of sempervirine supports this conclusion, at least for the β-carboline system (*cf.* Witkop, ref. 3).

The harman anhydronium base is slightly, but significantly, more basic than the norharman analog in accord with the usual effect of methyl substitution.[11] On the basis of the foregoing discussion it becomes tempting to suggest that the δ-carboline anhydronium base should have a dissociation constant almost as high as that of the β-isomer.

Acknowledgment.—The interest and encouragement of Dr. C. J. Cavallito was much appreciated, as was the capable assistance of Mr. Dean F. Cortright and Mr. Donald L. Miller in measuring the dissociation constants.

Experimental[12]

4-Chloropyridine.—The following modification of the reported procedures[7] was used. One hundred grams (1.05 moles) of pyridine N-oxide was heated in an oil-bath to 125–130°. The bath was removed and 245 g. (1.6 moles) of phosphorus oxychloride was added dropwise, with stirring, at such a rate as to maintain a vigorous evolution of gas. Stirring was continued and the reaction mixture was heated at 125–130° (oil-bath temperature) until the solution became clear (about 3 hr.). Excess phosphorus oxychloride was distilled out and the cooled solution was poured on cracked ice, made strongly alkaline and exhaustively extracted with ether. After drying and removal of the ether the residue was distilled to yield 16.0 g. of colorless liquid, b.p. 147–150°, $n^{25}D$ 1.5269, picrate m.p. 139–141° (reported for 4-chloropyridine, b.p. 147–148°, picrate m.p. 140–141°). A

(9) See for example A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., Second Edition, 1949, pp. 246–248.

(10) *Cf.* L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 256.

(11) For example see H. C. Brown and X. R. Mihm, THIS JOURNAL, **77**, 1723 (1955).

(12) Melting points are corrected for stem exposure. Microanalyses by the Clark Microanalytical Laboratories, Urbana, Illinois.

second, higher boiling fraction of 14.0 g. was obtained, b.p. 153–157°, picrate m.p. 131–136°, which was apparently a mixture of additional 4-chloropyridine and 2-chloropyridine. This decomposed on attempted refractionation.

5-Pyrid-4,3b-indole Methiodide.—γ-Carboline was synthesized from 4-chloropyridine as described by Robinson and Thornley.[4] The methiodide was prepared in ethanol and recrystallized from isopropyl alcohol–ethyl acetate; m.p. 231–232.5°.

Anal. Calcd. for $C_{12}H_{11}N_2I$: C, 46.47; H, 3.57; I, 40.92. Found: C, 46.63; H, 3.73; I, 40.66.

Other Materials.—Norharman methobromide, harman methobromide and α-carboline methiodide were analytically pure samples prepared as described earlier.[5]

pK_a Determinations.—Solutions of approximately 200 mg. of the salts in 50 ml. of carbon dioxide-free, 60% aqueous ethanol (0.01–0.015 *M*) were titrated with standard 0.1 *N* sodium hydroxide. *p*H measurements were made at 25° after each 0.2 ml. increment of the alkali, with a Model G Beckman *p*H meter.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Formation of Dihydrocarbostyril-3-acetic Acid and Esters by Rearrangement

BY H. A. LLOYD, LOUISE U. MATTERNAS AND E. C. HORNING

RECEIVED MAY 21, 1955

A study of the synthesis of heterocyclic systems through rearrangement reactions has been continued with an examination of an acid-catalyzed amide–ester exchange involving the transformation of a seven-membered lactam to a six-membered dihydrocarbostyril system.

The seven-membered lactam 2-oxo-5-carbethoxy-2,3,4,5-tetrahydrobenzazepine may be converted into a five-membered lactam, ethyl oxindole-3-propionate, by an acid-catalyzed intramolecular exchange reaction.[1] Since it is known that esters of oxindole-3-acetic acid undergo ring expansion to 2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid under similar conditions,[2] it may be concluded that the relative order of stability of these cyclic lactams is 6 > 5 > 7, in terms of the number of members in the heterocyclic ring. If this is correct, a suitably substituted seven-membered lactam should rearrange under acid-catalyzed conditions to form a dihydroquinolone.

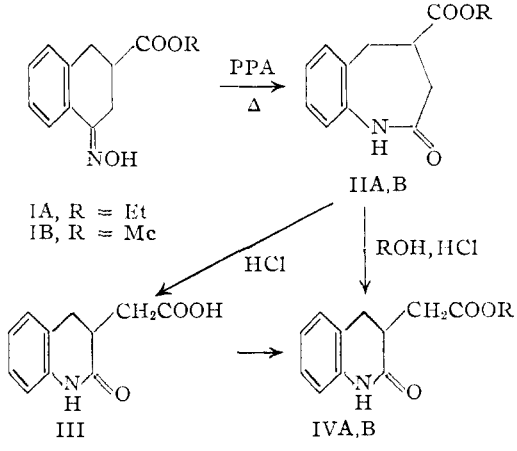
A ring contraction by amide–ester exchange was found to occur for 2-oxo-4-carbethoxy-2,3,4,5-tetrahydrobenzazepine (IIA) and the corresponding methyl ester IIB. These benzazepines were prepared by the Beckmann rearrangement of 3-carbethoxy- and 3-carbomethoxytetralone-1 oxime with polyphosphoric acid. The ester groups remained unchanged through the reaction. An intramolecular exchange reaction was carried out by heating the ester–amide in alcohol with hydrochloric acid, and the product in each case was an ester of dihydrocarbostyril-3-acetic acid (IVA, B). With concentrated hydrochloric acid, the reaction product was the corresponding acid III.

The relationship between the acid III and the ester IVB was confirmed by the esterification of the acid with diazomethane. This indicates that the acid III is indeed a dihydroquinolone rather than the isomeric seven-membered lactam-acid. A confirmation of the dihydroquinolone structure for the esters IVA, B was sought through dehydrogenation procedures. Through the use of a palladium–carbon catalyst, with or without a solvent, the ester IVA was dehydrogenated to a new substance through loss of two hydrogen atoms. This agrees with the properties expected for a dihydroquinolone; the product was ethyl carbostyril-3-acetate.

(1) H. A. Lloyd and E. C. Horning, THIS JOURNAL, **76**, 3651 (1954).

(2) P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, *ibid.*, **75**, 5305 (1953).

In the course of this work it was possible to make a number of comparisons of infrared spectra for seven- and six-membered lactam systems related to II and IV. In chloroform solution, the carbonyl–amide band in a seven-membered lactam system was found uniformly at 5.97 μ. This was true for 2-oxo-2,3,4,5-tetrahydrobenzazepine and its 4- and 5-substituted esters. The corresponding band for dihydrocarbostyrils, in chloroform solution, was at 5.95–5.97 μ. It therefore was not possible to follow the rearrangement by infrared measurements near 6 μ. For comparison, it may be noted that the carbonyl band of 1-ethyloxindole falls at 5.97 μ (chlf.). The oxindole acid and esters described in a previous paper show overlapping bands in the 5.77–5.97 μ range. For example, ethyl oxindole-3-propionate shows broad absorption over 5.77–5.87 μ (chlf.; in dilute solution the peak appears at 5.80 μ).



Experimental[3]

3-Carbethoxytetralone-1 Oxime (IA).—A 27-g. sample of 3-carboxytetralone-1[4] was esterified by heating a mixture of the acid, excess ethanol, benzene and a few drops of sul-

(3) All melting points were taken on a Kofler stage. Spectra measurements were carried out by Mrs. Iris Siewers. Analyses are by Dr. William Alford and his staff.

(4) E. C. Horning and G. N. Walker, THIS JOURNAL, **74**, 5148 (1952).