larger than the corresponding value of 1.314[7] for cinnamate hydrolysis in the same solvent, 87.8% ethanol. This difference, only a small part of which can be due to the different temperatures (20° *vs.* 30°) of the two studies, has been attributed[4,8] to an especially large "field effect" through the linear system. There then remains an uncertainty as to which systems may reasonably be expected to show this large effect.

It is surprising that phenylpropiolic acid and ester series do not show abnormal σ-values. If, in fact, transmission of electronic effects from the phenyl ring to the functional group is largely a "field" or inductive effect, this should be reflected in σ-values which approach Taft's σ^0 based on benzene derivatives having nonconjugated side-chain functional groups.[9] This does not appear to be true in the preceding cases, nor in the shielding of acetylenic protons in the phenylacetylenes.[10] Rates of alkaline hydrolysis of the ethyl phenylpropiolates have, therefore, been redetermined on a more extensive series than previously studied.[4] A lower temperature (10°) and greater dilution have been used to permit more accurate determination of these fast rates (Table I).

TABLE I

RATES OF ALKALINE HYDROLYSIS OF ETHYL PHENYLPROPIOLATES[a] IN 87.8% ETHANOL AT 10°

Substituent	$k \times 10^2$ l. mole^{-1} sec.$^{-1}$
p-CH_3	1.19
H	1.61
p-F	2.08[b]
p-Cl	3.13
m-Cl	4.48
p-NO_2	12.0

[a] Prepared by the methods of M. S. Newman and S. H. Merrill, *J. Am. Chem. Soc.*, **77**, 5552 (1955). Initial [KOH] = 0.02 *M*, [RCOOEt] = 0.012 *M*. The kinetic method is that reported in ref. 7. [b] *Anal.* Calcd. for $C_{11}H_9O_2F$: C, 68.74; H, 4.72. Found: C, 69.02; H, 4.90.

About 20% of the *p*-nitro ester is diverted to an ester of much lower reactivity, probably the ethoxycinnamate. Nevertheless, it has been possible to obtain consistent rate constants corresponding with more than 90% of the desired reaction. *The value of ρ is 1.10.* Five of the points (excepting H) of the plot of log *k vs.* ordinary σ-values fall on a straight line with such precision that no deviation is detectable graphically. The unsubstituted compound falls slightly off this line. All points have been weighed equally in determining ρ; the average deviation from the best line is about 0.01 σ-unit. Making use of σ-values derived from the saponification of ethyl cinnamates in 87.8% ethanol[11] the average deviation in σ is only 0.005 unit, which indicates a close correspondence of the resonance-inductive balance in the two systems. While it would have been desirable to include additional compounds having "reliable" *meta* substituents[12] in this study, it was not found possible to obtain by published procedures samples of sufficient homogeneity to increase confidence in the determined value of ρ.

(7) J. J. Bloomfield and R. Fuchs, *J. Org. Chem.*, **26**, 2991 (1961).
(8) R. E. Dessy and J.-Y. Kim, *J. Am. Chem. Soc.*, **83**, 1167 (1961).
(9) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).
(10) C. D. Cook and S. S. Danyluk, *Tetrahedron*, **19**, 177 (1963).
(11) K. Kindler, *Ber.*, **69**, 2792 (1936).
(12) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).

The earlier value of ρ for ethyl phenylpropiolate saponification, based on four points fitting with rather poor precision, appears to be in error.[13] *There is now no substantiated case in which the acetylenic unit transmits electronic effects better than, or, as well as, a trans ethylenic unit.*

Acknowledgment.—The author wishes to thank Dr. Jordan J. Bloomfield and Mr. Scott Cohen for furnishing several of the compounds.

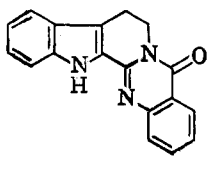
(13) The new value of ρ appears to give a much improved fit of Miller's ρ–ρ relationship. (S. I. Miller, unpublished studies.)

Investigations in Heterocycles. XIV. 2- and 3-Azaoctahydroindolo[2,3*a*]quinolizines[1]

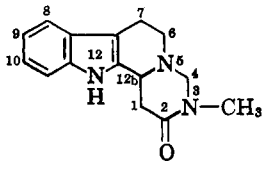
GEORGE DESTEVENS AND MARYLOU SKLAR

Research Department, Ciba Pharmaceutical Company, Division of Ciba Corporation, Summit, New Jersey

In a recent report[2] from our Laboratory, there was outlined the synthesis of a variety of tetracyclic and pentacyclic indolo[2,3*a*]quinolizines related to naturally occurring substances. It was of particular interest to prepare tetracyclic indolo[2,3*a*]quinolizines containing a nitrogen atom in ring E, compounds bearing a formal resemblance to Rutecarpine (I). Thus, as previously described,[2] II was converted to its N-methyl amide III which was allowed to react with formaldehyde in refluxing ethyl alcohol with a trace of alkaline catalyst to afford 3-methyl-3-aza-1,2,3,4-6,7,12,12b-octahydro-2-oxoindolo[2,3*a*] quinolizine (IV). It was also pointed out at the time that condensation of III with a variety of aromatic aldehydes yielded the corresponding 4-aryl derivatives of IV.



I



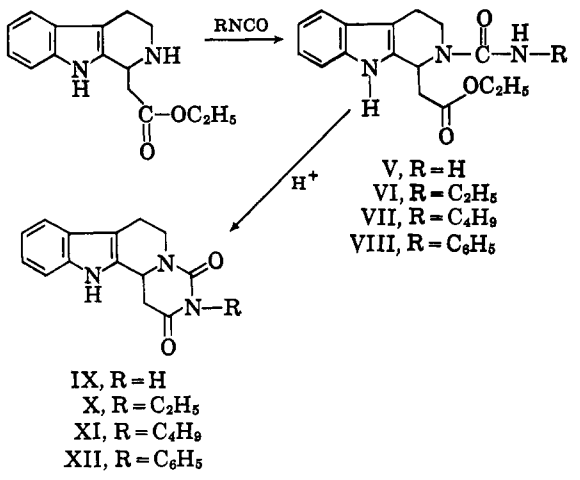
IV

It appeared now that a further extension to modifications of IV would be (a) the preparation of similar tetracyclic indoles with a keto group in position 4 and substituents other than a methyl group at the 3-aza position, and (b) the preparation of a 2-azaoctahydroindolo[2,3*a*]quinolizine. The synthesis of some of these compounds, as outlined in Scheme I, serves as the subject of this note.

Compound II proved very useful in these studies, since it readily underwent condensation with alkyl and aryl isocyanates in cyclohexane to form the corresponding urea derivatives which were converted to the 2,4-dioxo-3-substituted 3-azaoctahydroindolo[2,3*a*]quinolizine in refluxing ethyl alcohol containing small amounts

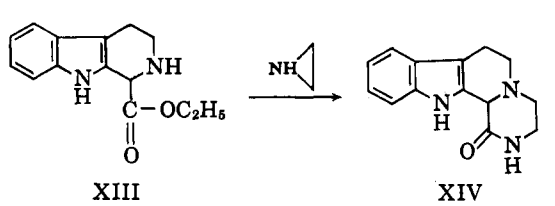
(1) This subject was discussed in part by G. deS. in a Symposium Lecture on the Chemistry of Nitrogen Heterocycles sponsored by the Medicinal Chemistry Division of the 141st National Meeting of the American Chemical Society, Washington, D. C., March 27, 1962.
(2) G. deStevens, H. Lukaszewski, M. Sklar, A. Halamandaris, and H. M Blatter, *J. Org. Chem.*, **25**, 2457 (1962).

SCHEME I



of hydrogen chloride. The 3-unsubstituted aza compound IX was prepared by the interaction of the hydrochloride of II with potassium cyanate to form V, followed by ring closure as described. It is noteworthy that the infrared spectrum of V was unusually different in the carbonyl region from the other urea derivatives when measured in Nujol mull. Compound V gave a strong band at 1695 cm.$^{-1}$ for the ester absorption, whereas the absorption of esters VI–VIII was at 1722 cm.$^{-1}$. However, the ester carbonyl absorption of V in chloroform solution was shifted to 1725 cm.$^{-1}$. Thus, at least for the unsubstituted urea intermediate, there exists significant intermolecular hydrogen bonding. The conversion of V to IX gave a substance whose spectrum contained two strong bands in the carbonyl region, one at 1705 cm.$^{-1}$ and the other at 1685 cm.$^{-1}$, which was typical of these 2,4-dioxooctahydroindolo-[2,3a]quinolizines.

Another modification of ring D was concerned with the synthesis of a 2-azaoctahydroindolo[2,3*a*]quinolizine. This was accomplished in one step merely by allowing 1-carbethoxy-1,2,3,4-tetrahydro-β-carboline (XIII) to react with ethyleneimine in refluxing ethyl alcohol. Ultraviolet absorption data preclude the



possibility that ring closure could have occurred on N_a since the major maximum for such substituted indole nitrogen compounds would be from 236–238 mμ.[3]

Several attempts were made to reduce the carbonyl group in XIV with lithium aluminum hydride to obtain a saturated ring D compound. However, this carbonyl proved to be very resistant to hydride reduction, and at best, only trace amounts of impure product were realized. Strong hydrogen bonding between N_a and the amide carbonyl, as illustrated with Dreiding models, offers a reasonable explanation for this lack of reactivity of the amide carbonyl.

(3) J. Pecher, R. H. Martin, N. Defay, M. Kaisin, J. Peeters, G. van Binst, N. Veryele, and F. Alderweireldt, *Tetrahedron Letters*, No. **8**, 270 (1961).

Experimental[4]

2-Carbamoyl-1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline (V).—1-Carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline hydrochloride[5] (2.7 g.) was dissolved in water warmed to 50°. This solution then was treated with 0.9 g. of potassium cyanate dissolved in 5 ml. of water, whereupon an immediate reaction occurred. A thick oil separated from solution. This oil was triturated well with distilled water and then taken up in ether. After drying the ether extract over sodium sulfate the drying salt was filtered off, and the filtrate was evaporated to dryness *in vacuo*. Trituration of the residue with ethyl alcohol resulted in the formation of a crystalline mass which was recrystallized from ethyl alcohol to yield a pure substance, m.p. 157–158°. Recrystallization of this substance from methyl alcohol gave a compound with identical chemical and physical properties. Infrared absorption in Nujol mull shows a strong band at 1695 cm.$^{-1}$ for the bonded ester group. In chloroform solution, this absorption band is shifted to 1725 cm.$^{-1}$. The carbamoyl absorption is evidenced at 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.65; H, 6.32; N, 13.90. Found: C, 63.35; H, 6.52; N, 13.70.

3-Aza-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3*a*]quinolizine (IX).—Two grams of V dissolved in 50 ml. of ethyl alcohol was treated with 10 ml. of ethyl alcohol saturated with hydrogen chloride, and the solution was refluxed on the steam bath for 4 hr. The solution was refrigerated overnight, and the resulting precipitate was collected on a filter. The light tan solid was recrystallized from excess ethyl alcohol to afford 1.1 g. of white crystals, which did not melt up to 350°. Infrared absorption in Nujol mull: 3300 (indole NH), 3150, and 3055 cm.$^{-1}$ (quinolizine NH); also strong absorptions at 1705 and 1685 cm.$^{-1}$ for 2,4-dioxoquinolizine grouping.

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.14; N, 16.46. Found: C, 65.62; H, 5.09; N, 16.35.

1-Carbethoxymethyl-2-ethylcarbamoyl-1,2,3,4-tetrahydro-β-carboline (IV).—A mixture of 2.6 g. (0.01 mole) of 1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline and 0.71 g. (0.01 mole) of ethyl isocyanate in 50 ml. of dry cyclohexane was heated at reflux temperature for 30 min. and chilled in an ice bath. The white precipitate which formed was collected and washed with a small amount of cyclohexane. Two recrystallizations from ethyl alcohol gave an 83% yield of white cubic crystals, m.p. 137°. Infrared absorption shows the principal band at 1722 cm.$^{-1}$ for ester group.

Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.03; H, 7.05; N, 12.60. Found: C, 64.88; H, 7.05; N, 12.39.

The following compounds were prepared in the same manner.

2-*n*-Butylcarbamoyl-1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline (VII), m.p. 131–133°, infrared absorption at 1720 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{20}H_{27}N_3O_3$: C, 67.21; H, 7.61; N, 11.76. Found: C, 67.34; H, 7.68; N, 11.54.

1-Carbethoxymethyl-2-phenylcarbamoyl-1,2,3,4-tetrahydro-β-carboline (VIII), m.p. 179–180°, infrared absorption at 1722 (ester carbonyl) and 1675 cm.$^{-1}$ (carbamoyl).

Anal. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.00; H, 6.14; N, 11.14. Found: C, 69.74; H, 6.17; N, 10.85.

The cyclization of compounds VI–VIII was carried out according to the previously described precedure for the preparation of IX. The compounds prepared are listed.

2,4-Dioxo-3-ethyl-3-aza-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3a]quinolizine (X), m.p. 184–185°.

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67,81; H, 6.05. Found: C, 67.48; H, 6.01.

3-*n*-Butyl-3-aza-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3*a*]quinolizine (XI), m.p. 140–141°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.39; N, 13.49. Found: C, 69.25; H, 6.42; N, 13.24.

2,4-Dioxo-3-phenyl-3-aza-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3*a*]quinolizine (XII), m.p. 196–197°, infrared absorption in Nujol mull at 3300–3450 (broad), 1690, 1640, 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{17}N_3O_2 \cdot C_2H_5OH \cdot H_2O$: C, 66.82; H, 6.37; N, 10.51. Found: C, 66.82; H, 6.00; N, 10.51.

2-Aza-1,2,3,4,6,7,12,12b-octahydro-1-oxoindolo[2,3*a*]quinolizine (XIV).—Four grams of 1-carbethoxy-1,2,3,4-tetrahydro-β-

(4) All melting points reported herein are uncorrected.

(5) G. B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959).

carboline[6] and 0.040 g. of the hydrochloride salt of the above ester were dissolved in 25 ml. of refluxing ethyl alcohol. Ethyleneimine (0.67 g.) dissolved in 10 ml. of ethyl alcohol was added dropwise to the refluxing solution and this heating was continued for 24 hr. On chilling, this solution deposited light yellow crystals which were collected on a Büchner funnel, washed with ethyl alcohol, and then recrystallized from an excess of that solvent. One gram of pure product, m.p. 234–235° dec., was obtained. Infrared absorption shows a strong broad band at 3400 cm.$^{-1}$ (overlap of indole and amide NH) and a strong amide band at 1670 cm.$^{-1}$; $\lambda_{max}^{C_2H_5OH}$ 224 mμ (ε 36,190), 278 (39,340), 289 (6,360).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.26; H, 17.42. Found: C, 69.95; H, 6.29; N, 17.57.

Acknowledgment.—The authors extend their sincere thanks to Dr. E. Schlittler for his continuing interest. We are also indebted to Mr. L. Dorfman and his associates for the microanalytical and spectral data.

(6) F. J. Vejdeiek, V. Treka, and M. Protiva, *J. Med. Pharm. Chem.*, **3**, 427 (1961).

A Synthesis of 6-Methyl-2-phenyl-5-azacycl[3.2.2]azine and Related Compounds[1,2]

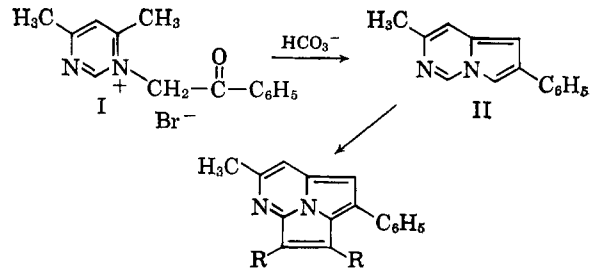
V. BOEKELHEIDE AND S. S. KERTELJ

Department of Chemistry, University of Oregon, Eugene, Oregon

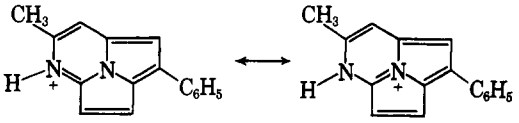
Received June 14, 1963

The reaction of pyrrocolines with dimethyl acetylenedicarboxylate,[3–5] an early example of a general procedure now known as the 1,3-dipolar addition reaction,[6] provides convenient access to cycl[3.2.2]azine and its various derivatives. Although the central nitrogen of cycl[3.2.2]azine is not basic, nitrogen atoms placed in the perimeter are basic and allow for the preparaton of the corresponding quaternary salts which are more suitable for physiological testing.[7] It was for this reason that work was initiated on the synthesis of 5-azacycl[3.2.2]azine derivatives. However, since then studies on the correlation of molecular orbital calculations with experimental data on the electronic spectra and basicity of the cyclazines has made it desirable to have additional examples with nitrogen in the periphery as an aid to evaluating the parameter to be assigned to nitrogen.[8,9]

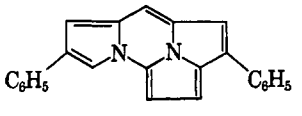
As starting material, 4,6-dimethylpyrimidine was converted in 97% yield to the corresponding quaternary bromide I using phenacyl bromide in benzene at room temperature. Cyclization by the Chichibabin procedure[10] gave 7-methyl-2-phenyl-6-azapyrrocoline(II) in 56% yield. Treatment of II with dimethyl acetylenedicarboxylate in the presence of a palladium-on-charcoal catalyst and toluene then led to the corresponding 5-azacycl[3.2.2]azine III in 28% yield. Hydrolysis of the diester with base proceeded essentially quantitatively to give the diacid IV. Finally, decarboxylation of the diacid using copper powder and aniline occurred smoothly in 78% yield to produce the desired 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (V).



As expected, 6-methyl-2-phenyl-5-azacycl[3.2.2]azine was readily soluble in aqueous acid. However, its ultraviolet and visible absorption spectrum showed an unexpected shift to longer wave lengths in the presence of acid. Thus, in neutral ethanol V showed maxima at 227 (4.26), 264 (4.54), 327 (4.34), and 452 mμ (log ε 3.59), whereas in 0.09 *M* hydrochloric acid maxima were observed at 227 (4.22), 268 (4.55), 366 (4.33), and 473 mμ (log ε 3.31). This shift becomes understandable, however, when it is considered that V, on protonation, is a resonance hybrid with contributing structures such as VI and VII.



In the original plan the presence of the methyl group at the 6-position of V was desired so that a second Chichibabin ring closure could be effected to give the interesting fused bispyrrocoline represented by VIII. Unfortunately, attempts to accomplish this ring closure were unsuccessful.



Experimental[11]

1-Phenacyl-4,6-dimethylpyridinium Bromide (I).—A solution of 11.0 g. of 4,6-dimethylpyrimidine and 21.0 g. of phenacyl bromide in 60 ml. of benzene was allowed to stand at room temperature for 10 days. The orange-yellow precipitate, which separated, was collected by filtration, washed with benzene, and air-dried. This gave 31.4 g. (97%) of product of sufficient purity for use in the next step. Recrystallization of the orange-yellow solid from absolute ethanol gave 23.0 g. (71%) of yellow crystals, m.p. 173° dec.

Anal. Calcd. for $C_{14}H_{15}N_2OBr$: C, 54.73; H, 4.92; N, 9.12; Br, 26.01. Found: C, 54.38; H, 4.95; N, 8.84; Br, 25.94.

7-Methyl-2-phenyl-6-azapyrrocoline (II).—To a stirred solution of 10.5 g. of the crude quaternary bromide I in a mixture of 50 ml. of ethanol and 350 ml. of water there was added a saturated

(1) Abstracted from the M.S. thesis of S. S. Kertelj, University of Oregon, 1963.

(2) Aided in part by the National Science Foundation and by the U. S. Army Research Office (Durham).

(3) J. C. Godfrey, *J. Org. Chem.*, **24**, 581 (1959).

(4) A. Galbraith, T. Small, and V. Boekelheide, *ibid.*, **24**, 582 (1959).

(5) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 453 (1961).

(6) R. Huisgen and A. Eckell, *Tetrahedron Letters*, **12**, 5 (1960); *cf.* R. Huisgen, "Theoretische Chemie und Organische Synthese," Festschrift der Zehnjahresfeier des Fond der Chemischen Industrie, Düsseldorf, Germany, 1960.

(7) V. Boekelheide and A. Miller, *J. Org. Chem.*, **26** 431 (1961).

(8) V. Boekelheide, F. Gerson, E. Heilbronner, and D. Meuche, *Helv. Chim. Acta*, in press.

(9) F. Gerson, E. Heilbronner, N. Joop, and H. Zimmermann, *ibid.*, in press.

(10) A. E. Chichibabin, *Ber.*, **59**, 2048 (1926).

(11) Microanalyses by Micro-Tech Laboratories and F. Pascher. Melting points are uncorrected.