The Preparation of Derivatives of 9-Oxo-2,3,4,9-tetrahydro-1*H*-pyrrolo[3,4-*b*]quinoline and 7-Oxo-7,9,10,11-tetrahydro-8*H*-benzo[*h*]pyrrolo[3,4-*b*]quinoline (1)

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We recently reported the facile preparation of 1,2-dihydro-3-oxo-3*H*-pyrrolo[3,4-*b*]quinoline derivatives from 2,3-dioxopyrrolidines through application of the Friedlander and Pfitzinger syntheses (2). We now wish to describe efficient methods of preparation of 9-oxo derivatives in the same heterocyclic series by application of the Conrad-Limpach reaction (3) to "anils" of easily-accessible 4-carbethoxy-3-pyrrolidinone derivatives such as the compounds represented by formulas I and VI. The reactions of "anil" formation and Conrad-Limpach cyclization are those represented by the equations shown in Chart I. By use of aniline or aniline derivatives 9-oxo-2,3,4,9-tetrahydro-1*H*-pyrrolo[3,4-*b*]quinoline derivatives of types III and VIII were obtained; by use of α-naphthylamine

CHART I

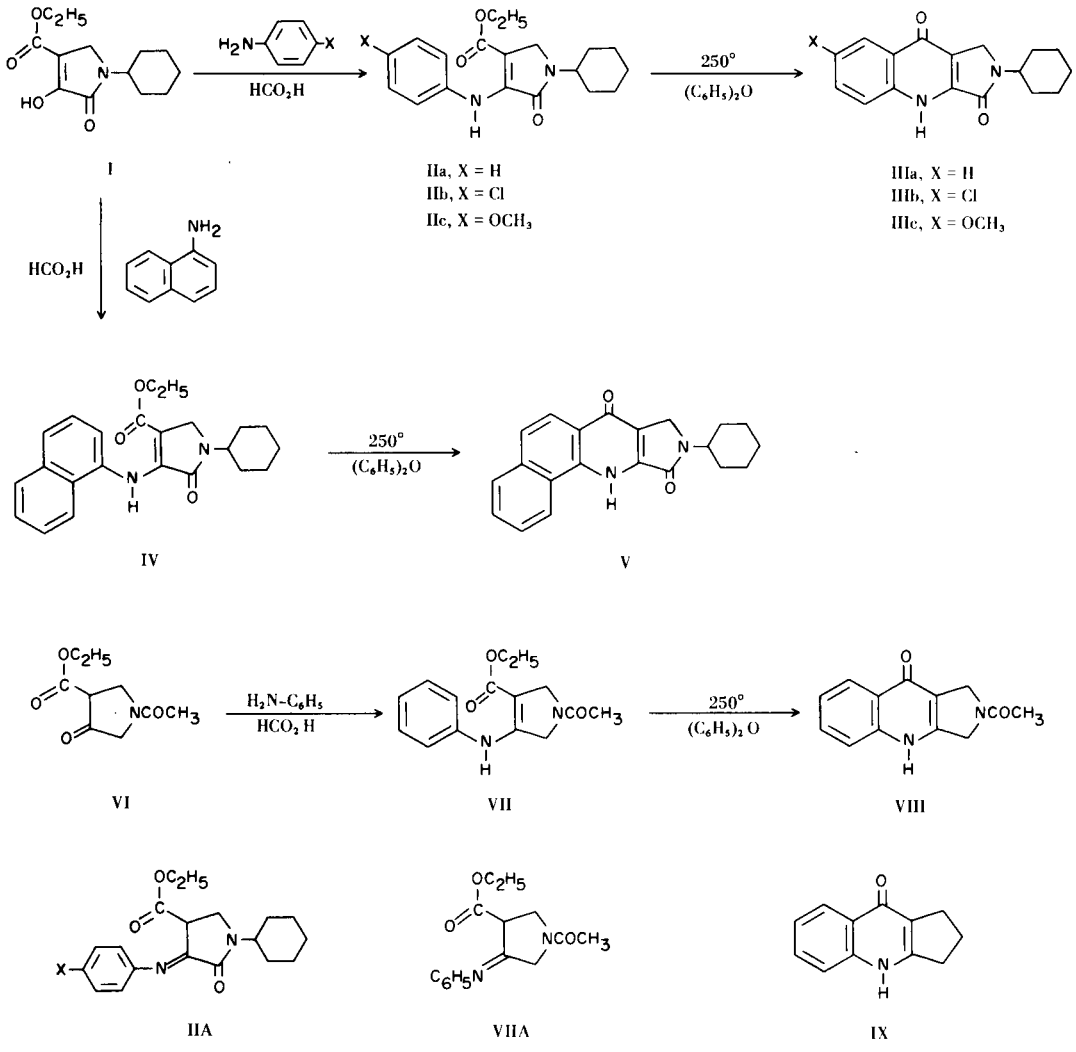
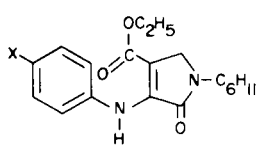
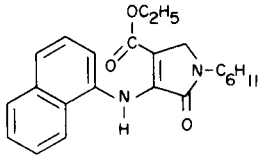


TABLE I

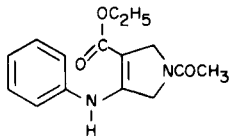
3-Arylamino-3-pyrroline Derivatives



IIa, X = H
IIb, X = Cl
IIc, X = OCH_3



IV



VII

Compound	Yield	Molecular Formula	M.p., °C	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	84.9%	$C_{19}H_{24}N_2O_3$ (a)	135-136	69.49	7.37	8.53	69.44	7.36	8.32
IIb	77.3%	$C_{19}H_{23}ClN_2O_3$ (b)	152-153	62.88	6.38	7.72	62.87	6.41	7.54
IIc	65.5%	$C_{20}H_{26}N_2O_4$ (c)	100-101	67.02	7.31	7.82	66.93	7.46	7.58
IV	84.6%	$C_{23}H_{26}N_2O_3$ (d)	174-175	72.99	6.93	7.40	73.05	6.88	7.20
VII	53.8%	$C_{15}H_{18}N_2O_3$ (e)	121-122	65.67	6.61	10.21	65.92	6.67	9.98

(a) Ir (Nujol) μ 3.05, 5.95, 6.00, 6.15, 6.54, 7.43, 8.20, 8.90, 9.76, 10.25, 11.20, 12.85, 13.10, 13.30, 14.20, 14.50. (b) Ir (Nujol) μ 3.05, 5.95, 5.99, 6.10, 6.30, 6.51, 8.18, 8.88, 9.80, 11.20, 11.85, 12.0, 12.35, 12.82, 13.10, 13.75, 14.78. (c) Ir (Nujol) μ 3.05, 5.95, 6.00, 6.13, 6.50, 8.15, 8.90, 9.71, 11.20, 11.95, 12.75, 13.10, 13.71, 14.12. (d) Ir (Nujol) μ 3.10, 5.95, 5.99, 6.10, 6.55, 7.90, 8.18, 8.90, 9.31, 9.90, 12.61, 12.80, 12.90, 13.21, 13.55, 14.48. (e) Ir (Nujol) μ 3.00, 5.80, 6.02, 6.15, 6.22, 7.90, 8.18, 8.60, 9.51, 10.30, 11.00, 11.66, 13.05, 13.65, 14.38.

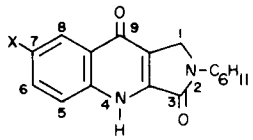
a 7-oxo-7,9,10,11-tetrahydro-8*H*-benzo[*h*]pyrrolo[3,4-*b*]-quinoline derivative (V) representative of a new heterocyclic system was secured. Methods for the preparation of compound I and other 1-substituted-4-carbethoxy-2,3-dioxopyrrolidines (4) and for compound VI and other 1-acyl-4-carbethoxy-3-pyrrolidinones (5) have been described previously.

The reaction of the pyrrolidinone derivatives I and VI with primary aromatic amines to yield "anils" of types II, IV or VII was carried out by use of a uniform procedure which employed formic acid catalysis in refluxing ethanol solutions, with yields in the range 54-85%. These products yielded infrared spectra (see footnotes to Table I) indicative of the tautomeric structures represented by the 3-anilino-3-pyrroline formulas II, IV and VII. The bands in the range 3.00-3.10 μ showed that an N-H function was present, thereby eliminating from consideration true anil (imine) tautomers, as represented by formulas such as IIA or VIIA. The thermal cyclizations to 4-quinolone derivatives of types III, V and VIII were also conducted by means of a single procedure in which diphenyl ether solutions of the 3-anilino-3-pyrroline derivatives were held at temperatures in the range 245-250° for one-half hour, as suggested by Conrad-Limpach cyclizations reported by Ewing and Steck (6) and Witkop, Patrick and Rosenblum (7). Yields in this step ranged from 57 to 99%. The infrared, ultraviolet and nuclear magnetic resonance spectra of these products (see footnotes to Table II) (8) were all fully consistent with the formulas given in Chart I.

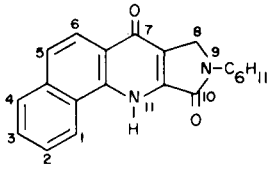
It was of some interest that compound VIII was soluble in dilute aqueous sodium hydroxide, whereas compounds IIIa, IIIb, IIIc and V were not. In order to ascertain whether this result might perhaps signify that VIII was an actual 4-hydroxyquinoline derivative, whereas the other compounds had the expected 4-quinolone structures, ultraviolet spectra were determined. Results are recorded in Table III. The spectrum of compound VIII was virtually identical to a published spectrum (7) for 2,3-cyclopenteno-4-quinolone (IX), and the spectrum of compound IIIa shows three principal bands above 220 mμ in the same relationship with remarkably little change introduced by the carbonyl group in position 3 except for a bathochromic shift. The characteristic bifurcation of the long wavelength maximum of 4-quinolones (6) was observed in all of the spectra. The spectroscopic results offer no support for the conclusion that compound VIII exists principally in a tautomeric form different from compounds of type III or IX.

TABLE II

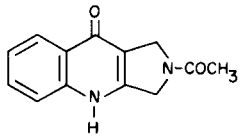
2-Acetyl-9-oxo-2,3,4,9-tetrahydro-1*H*-pyrrolo[3,4-*b*]quinoline (VIII), 2-Cyclohexyl-3,9-dioxo-2,3,4,9-tetrahydro-1*H*-pyrrolo[3,4-*b*]quinolines (III) and 9-Cyclohexyl-7,10-dioxo-7,9,10,11-tetrahydro-8*H*-benzo[*h*]pyrrolo[3,4-*b*]quinoline (V)



IIIa, X = H
IIIb, X = Cl
IIIc, X = OCH_3



V



VIII

Compound	Yield	Molecular Formula	M.p., °C	Analysis Calcd. C	H	N	Found C	H	N
IIIa	97.0%	$C_{17}H_{18}N_2O_2$ (a)	316-318	72.34	6.43	9.92	72.16	6.65	9.78
IIIb	57.3%	$C_{17}H_{17}ClN_2O_2$ (b)	>355	64.45	5.40	8.84	64.11	5.64	8.66
IIIc	74.5%	$C_{18}H_{20}N_2O_3$ (c)	327-328	69.21	6.45	8.97	68.93	6.68	8.93
V	99.0%	$C_{21}H_{20}N_2O_2$ (d)	320-321	75.88	6.07	8.43	75.92	6.08	8.15
VIII	80.3%	$C_{13}H_{12}N_2O_2$ (e)	330-333	68.41	5.30	12.27	68.60	5.19	12.20

(a) Ir (Nujol) μ 3.21, 6.00, 6.15, 6.31, 7.92, 8.24, 12.50, 13.07, 13.20, 14.11, 14.50, 14.75; nmr τ 1.91-2.85 (m, 4, benzo group), 5.48 (s, 2, methylene at position 1), 6.03 (m, 1, methine of cyclohexyl), 7.90-9.00 (m, 10, cyclohexyl). (b) Ir (Nujol) μ 3.25, 6.00, 6.18, 6.35, 8.00, 8.25, 12.10, 13.00, 13.51, 13.72, 14.45, 14.65; nmr τ 2.00 (s, 1, benzo group), 2.45 (s, 2, benzo group), 5.41 (s, 2, methylene at position 1), 6.00 (methine of cyclohexyl), 7.91-9.00 (m, 10, cyclohexyl). (c) Ir (Nujol) μ 3.20, 6.00, 6.12, 6.31, 7.92, 8.20, 8.30, 9.11, 9.70, 11.85, 12.35, 12.78, 13.20, 13.40, 14.45; nmr τ 2.40-2.91 (m, 3, benzo group), 5.43 (s, 2, methylene at position 1), 6.01 (m, 1, methine of cyclohexyl), 6.21 (s, 3, OCH_3 at position 7), 7.91-9.00 (m, 10, cyclohexyl). (d) Ir (Nujol) μ 3.05, 5.98, 6.12, 6.22, 6.50, 8.00, 8.12, 11.21, 12.18, 12.65, 13.13, 13.30, 14.35; nmr τ 1.83-2.30 (m, 6, naphtho group), 5.21 (s, 2, methylene at position 8), 5.80 (m, 1, methine of cyclohexyl), 7.90-9.00 (m, 10, cyclohexyl). (e) Ir (Nujol) μ 2.82, 6.08, 6.15, 6.40, 6.65, 7.98, 8.27, 9.72, 10.27, 11.98, 12.30, 12.95, 13.15, 13.42, 14.52; nmr τ 1.70-2.20 (m, 4, benzo group), 4.30 (m, 2, methylene at position 3), 4.82 (s, 2, methylene at position 1), 7.31 (s, 3, acetyl at position 2).

TABLE III

Ultraviolet Data

Compound	λ max, nm (log ϵ) (a)	λ min, nm
VIII	240 (4.49), 315 (4.09), 328 (4.14)	220, 265, 322
IX (7)	238 (4.48), 317 (4.09), 331 (4.13)	222, 261, 323
IIIa	245 (4.57), 333 (4.13), 348 (4.41)	225, 298, 341

(a) Data recorded for the range 220-390 nm. All curves exhibited several points of inflection not listed in the table.

EXPERIMENTAL (9)

Preparation of 3-Arylamino-3-pyrroline Derivatives (II, IV or VII).

Mixtures prepared from a 0.01-mole quantity of 4-carbethoxy-1-cyclohexyl-2,3-dioxopyrrolidine (I) (4) or 1-acetyl-4-carbethoxy-3-pyrrolidinone (VI) (5), a 0.012-mole quantity of the aromatic amine, 0.6 ml. of formic acid and 30 ml. of absolute ethanol were heated under reflux for 16 hours. The solutions were concentrated by distillation to approximately 10 ml. and diluted with water while hot until a faint turbidity appeared. The products, which crystallized from the mixtures upon cooling, were collected by filtration and purified by recrystallization from ethanol-water mixtures. The yields, melting points and infrared data are recorded in Table I.

Conrad-Limpach Cyclizations of 3-Arylamine-3-pyrroline Derivatives to Compounds of Types III, V and VIII.

The 3-arylamino-3-pyrroline derivatives (II, IV or VII) (2.0 g.) were heated in diphenyl ether (20 ml.) at 245-250° under a nitrogen atmosphere for ½ hour. When the resulting clear solutions were cooled, the products separated as crystalline solids, which were collected by filtration. An additional quantity of product precipitated and was filtered out following the addition of petroleum ether (b.p. 30-60°) to the filtrate. All of these products were crystallized from ethanol except for the 7-chloro derivative IIIb, for which the crystallization solvent was dimethylformamide. The yields, melting points and spectral data are recorded in Table II.

REFERENCES

(1) Supported in part by research grants (GM-04371) from the National Institutes of Health, U.S. Public Health Service.

(2) R. Madhav and P. L. Southwick, *J. Heterocyclic Chem.*, 9, 443 (1972).

(3) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N.Y., 1952, Chapter 1.

(4) P. L. Southwick, E. P. Previc, J. Casanova, Jr. and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(5) Y. H. Wu, W. G. Lobeck, and R. F. Feldkamp, *J. Med. Pharm. Chem.*, **6**, 762 (1962).

(6a) G. W. Ewing and E. A. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946); (b) E. A. Steck, G. W. Ewing and F. C. Nachod, *ibid.*, **71**, 238 (1949).

(7) B. Witkop, J. B. Patrick and M. Rosenblum, *ibid.*, **73**, 2641 (1949).

(8) Nuclear magnetic resonance spectra were determined on a Perkin-Elmer Hitachi R-20 instrument by use of solutions prepared in a 3:1 (by volume) deuteriochloroform-trifluoroacetic acid mixture.

(9) Microanalyses are by M-H-W Laboratories, Garden City, Michigan. Melting points were determined with a Mel-Temp apparatus in capillary tubes and are corrected.