droxide octahydrate (1.3 g.) in a mixture of water (5 ml.) and ethanol (2 ml.), and the mixture was heated on a steam bath for 3.5 hr. The precipitated salt was filtered off and washed well with alcohol and ether and dried. The resulting pale yellow solid (1.68 g.) was suspended in ether, 6 *N* hydrochloric acid (5 ml.) was added, and the mixture was shaken in a separatory funnel. The salt dissolved, the ether layer was separated, and the aqueous layer was extracted thoroughly with ether (six 15-ml. portions). The combined ethereal extracts were dried and the solvent was evaporated to give 0.48 g. (59%) of a brown solid, m.p. 145–152° dec., which could not be satisfactorily purified further.

Method B. A mixture of quinoxaline-2-carboxaldehyde (1.58 g., 0.01 mole), malonic acid (1.04 g., 0.01 mole), and ethanolic ammonia (1.25 ml. of concentrated NH_4OH in 15 ml. of ethanol; 0.02 mole of ammonia) was heated in a water bath held at 60° for 1.5 hr. The ethanol was evaporated to leave a black residue which partially dissolved in dilute sodium hydroxide. The alkaline solution was filtered to remove a small amount of insoluble material and the filtrate was treated with charcoal and acidified with 2 *N* sulfuric acid to give 0.31 g. (13%) of product as a deep brown solid, m.p. 143–153° dec., identical with that prepared by method A.

β-2-Quinoxalinylpropenoic Acid (**5c**). *Method B.* A solution of the diacid **17** (1.0 g.) in pyridine (10 ml.) containing piperidine (0.5 ml.) was refluxed for 1 hr. and the brown solution was poured into water. The precipitated solid was filtered off and dissolved in dilute sodium hydroxide solution, the solution was treated with charcoal and filtered, and the filtrate was acidified to give 0.40 g. (44%) of β-2-quinoxalinylpropenoic acid, m.p. 235–240° dec., as a chocolate brown powder, identical with a sample prepared from the chloral adduct **6c** with base, as described above (method A).

Method C. A mixture of the aldehyde (1.0 g.), malonic acid (1.5 g.), and piperidine (0.1 ml.) in pyridine (10.0 ml.) was heated on a steam bath for 1.5 hr. and the reaction mixture was poured into water. The black, precipitated solid (0.47 g., 40%) was filtered off, dissolved in dilute sodium hydroxide solution, and treated with charcoal, and the filtered solution was acidified to give 0.39 g. of β-2-quinoxalinylpropenoic acid (**5c**) as a brown solid, m.p. 235–240° dec., identical with the products prepared by methods A and B.

Ethyl α-Carbethoxy-β-2-quinoxalinylpropanoate (**19**). A solution of ethyl α-carbethoxy-β-2-quinoxalinylpropenoate (**16**, 2.0 g.) in ethanol (75 ml.) was hydrogenated at 40 p.s.i. of hydrogen using 10% palladium-on-charcoal (0.5 g.) catalyst. Removal of the catalyst and evaporation of the solvent left a pale yellow oil (1.8 g.) which could not be obtained crystalline; it decomposed on attempted distillation at high vacuum and was not purified further.[12c]

β-2-Quinoxalinylpropanoic acid (**3c**) was prepared by hydrolysis and decarboxylation of **19** according to the published procedure.[12c] From 1.80 g. of the diester **18** there was obtained 0.97 g. (78%) of β-2-quinoxalinylpropanoic acid, m.p. 110–114°, identical with a sample prepared by reduction of β-2-quinoxalinylpropenoic acid.

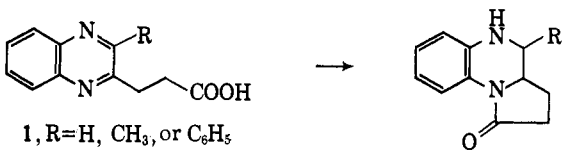
Facile Reductive Cyclizations. New Routes to Heterocycles. II[1]

Edward C. Taylor, Alexander McKillop, and Robert E. Ross[2]

Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey. *Received October 9, 1964*

A remarkably facile synthesis of the tricyclic diamides (**4a** *and* **b**) *has been found to result from treatment of 2-(2-carboxyethyl)- and 2-(3-carboxypropyl)-3(4H)-quinoxalone* (**3a** *and* **b**) *with sodium borohydride, followed by acidification. Attempted extension of this reaction to the 4-carboxybutyl, 5-carboxypentyl, and 6-carboxyhexyl derivatives* (**3c**, **d**, *and* **e**) *was unsuccessful. A general synthetic route to the above homologous series of quinoxalinyl-substituted alkanoic acids consisted of ethoxalylation of diesters of the type* $EtOOC(CH_2)_nCOOEt$ *followed by condensation with o-phenylenediamine, hydrolysis, and decarboxylation. A more direct synthetic route to the acids* (**3a–e**) *involving condensation of o-phenylenediamine with α-keto dibasic acids was found to be less satisfactory.*

During an investigation of synthetic routes to new condensed heterocyclic systems it was found that reduction of β-quinoxalinylpropanoic acids (**1**) with hydrogen in the presence of Raney nickel led directly to tricyclic pyrrolo[1,2-*a*]quinoxalone derivatives (**2**).[3] This



1, R=H, CH_3, or C_6H_5 → **2**, R=H, CH_3, or C_6H_5

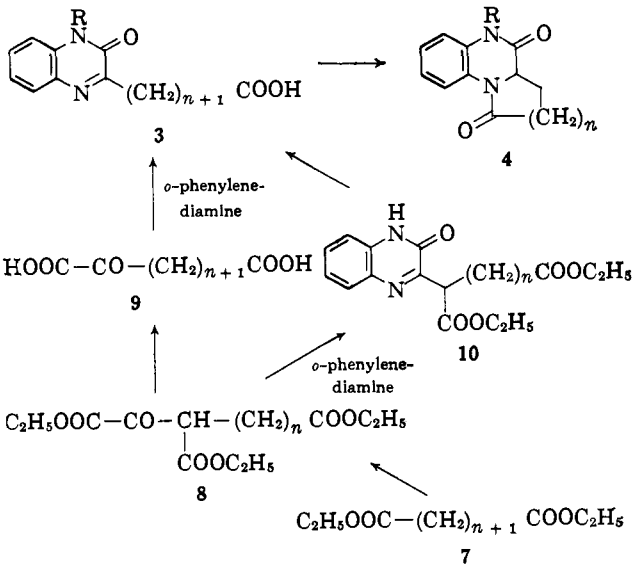
reductive cyclization proceeded under mild conditions and in high yield, thus providing for study a series of hithertofore unavailable heterocyclic compounds.

(1) This work was supported by a grant to Princeton University from the American Cancer Society.

(2) National Institutes of Health Predoctoral Fellow, 1963–1965.

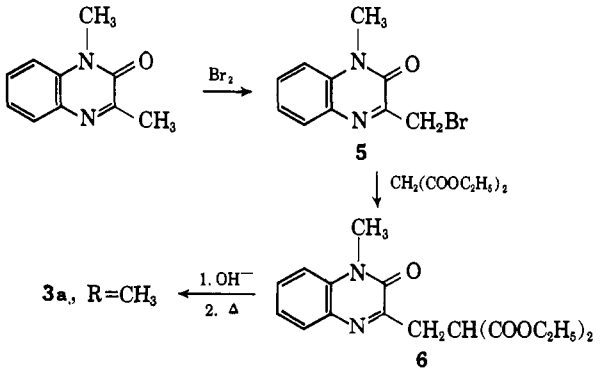
(3) Part I: E. C. Taylor and A. McKillop, *J. Am. Chem. Soc.*, **87** 1984 (1965).

We report in this paper extensions of these cyclization reactions to oxygenated derivatives of type **3** and, in particular, a remarkably facile method for the reductive cyclization of **3** to **4** which employs sodium borohydride in dilute sodium hydroxide solution.



a, $n=1$
b, $n=2$
c, $n=3$
d, $n=4$
e, $n=5$

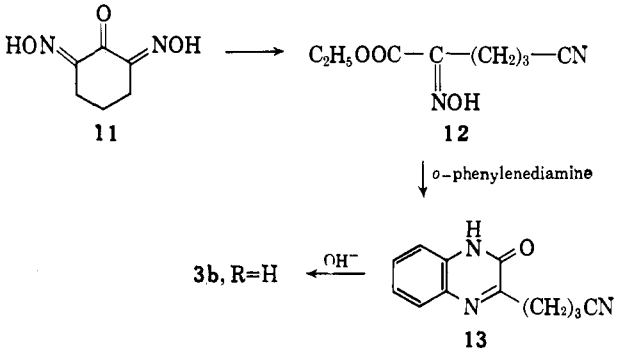
Synthesis of Intermediates. The first member of the series of type **3**, 2-(2-carboxyethyl)-3(4H)-quinoxalone (**3a**, R = H), was readily prepared by condensation of *o*-phenylenediamine with α-ketoglutaric acid.[4] Methylation with dimethyl sulfate in dilute potassium hydroxide solution gave the N-methyl derivative **3a** (R = CH_3). This latter compound was prepared[5] alternatively but laboriously by reaction of *o*-phenylenediamine with ethyl pyruvate to give 2-methyl-3(4H)-quinoxalone, followed by methylation with dimethyl sulfate in dilute potassium hydroxide to give 2,4-dimethyl-3(4H)-quinoxalone, monobromination to give **5**, and then alkylation with diethyl malonate to the substituted malonic ester **6**. This ester, on hydrolysis and decarboxylation, yielded the propanoic acid derivative **3a** (R = CH_3) identical with the product obtained as outlined above.



While the above method might be applicable in theory to the preparation of the desired homologous acids (**3b–e**), its scope is severely limited by the availability of the requisite α-ketodicarboxylic acids (**9b–e**) homologous with α-ketoglutaric acid. The generally employed method for preparation of α-ketodicarboxylic acids (**9**) involves the Claisen condensation of a dicarboxylic acid diester with diethyl oxalate to give the 2-ethoxalyl derivative **8** which on hydrolysis and decarboxylation yields an α-keto diacid **9**.[6] Treatment of diethyl succinate (**7a**) with diethyl oxalate proceeds in excellent yield,[6] but as the value of *n* increases complications due to side-reactions (and in particular to intramolecular cyclization) arise. Even though optimum conditions for these reactions have apparently been determined,[7–9] yields of the desired ethoxalyl derivatives **8** do not exceed 50–80%. The subsequent conversion of these intermediates to the α-keto diacids **9** by hydrolysis and decarboxylation proceeds well in the case of the first member of the series, **8a**, but is not satisfactory (yields of less than 50%) with the higher members of the series. A general objection to the use of α-keto diacids lies in the difficulty encountered in their isolation and purification. All members of the homologous series **9** are extremely soluble in water and alcohol and rather insoluble in the common organic solvents, which makes crystallization and purification troublesome.

It was found, however, that condensation of *o*-phenylenediamine with the intermediate 2-ethoxalyl derivatives (**8a–e**) gave the quinoxalones (**10a–e**) in excellent yield (75–95%). Hydrolysis of these diesters with alkali proceeded smoothly with concomitant decarboxylation to give the desired acids (**3a–e**), again in excellent yield (80–95%). This alternative synthesis thus obviates the difficulties inherent in the use of the free α-keto diacids.

An alternative synthesis of 2-(3-carboxypropyl)-3-(4H)-quinoxalone (**3b**, R = H) commenced with 1,2,3-cyclohexanetrione 1,3-dioxime (**11**).[10a] A second-order Beckmann rearrangement, brought about by the action of acetic anhydride and sodium ethoxide, resulted in the formation of ethyl 5-cyano-2-oximinopentanoate (**12**) which was condensed with *o*-phenylenediamine in acetic acid to give 2-(3-cyanopropyl)-3(4H)-quinoxalone

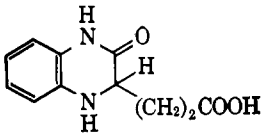


(4) R. Pohloudek-Fabini and E. Papke, *Pharmazie*, **18**, 273 (1963).
(5) This alternate synthesis of **3a** (R = CH_3) was accomplished by Dr. G. W. H. Cheeseman.
(6) L. Friedman and E. Kosower, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 510.
(7) W. Wislicenus and A. Schwanhäuser, *Ann.*, **297**, 110 (1897).
(8) H. Gault, *Bull. soc. chim. France*, 11, 382 (1912).
(9) F. Adickes, *Chem. Ber.*, **58**, 211 (1925).
(10) (a) A. Treibs and A. Kuhn, *Chem. Ber.*, **90**, 1693 (1957); (b) A. F. Ferris, *J. Org. Chem.*, **25**, 12 (1960); (c) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. K. Latourette, *ibid.*, **25**, 492 (1960); (d) A. F. Ferris, G. S. Johnson, and F. E. Gould, *ibid.*, **25**, 496 (1960); (e) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. Stange, *ibid.*, **25**, 1302 (1960).

(13). Hydrolysis then gave the desired butanoic acid derivative **3b** (R = H). Attempted extensions of this synthetic sequence to the preparation of the acids **3c** (R = H) and **3d** (R = H) through use of the readily available cycloheptanone and cyclooctanone were unsuccessful because of difficulties encountered in the preparation of the requisite dioximes.

Reductive Cyclization. Initial efforts at reductive cyclization of the quinoxalone derivatives **3a–e** (R = H) were focussed upon the first and most accessible member of the series, 2-(2-carboxyethyl)-3(4H)-quinoxalone (**3a**, R = H). Reduction with hydrogen and Raney nickel in alkaline solution under conditions analogous to those previously employed for the conversion of **1** to **2** gave moderate and varying yields (40–70%) of the desired tricyclic diamide **4a** (R = H). Yields of the tricyclic diamide **4a** (R = H) were uniformly low when ethanol, acetic acid, or acetic anhydride were used as solvent in the reduction step, and isolation of the reductive cyclization product in the presence of unchanged starting material (always present) was tedious. Reduction of **3a** (R = H) with zinc and acetic acid also led to the cyclization product in modest yield (40–50%), but again isolation and purification of the product posed experimental difficulties.

Consideration of the probable course of the reductive cyclization provides a plausible explanation for these unsatisfactory results. The obvious precursor to cyclic lactam formation must be the immediate reduction product, the 1,2-dihydro derivative **14**. Lactam formation can proceed only in acidic solution, as has been



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demonstrated previously in studies dealing with the reductive cyclization of β-quinoxalinylpropanoic acids of type **1**.[3] The intermediates in the latter case are, however, tetrahydroquinoxalines, which are known to be relatively stable both under acidic and basic conditions,[11] while the dihydroquinoxalone intermediates in the reductive cyclization of **3a–e** (R = H) to **4a–e** (R = H) are extremely unstable toward air oxidation, particularly in alkaline solution.[12] Considerable reoxidation of the dihydro intermediate **14** to starting material must take place during the time involved in removal of the hydrogenation catalyst and acidification of the reaction mixture, thus providing a reasonable explanation for the extensive contamination of the reaction product with (apparently) unchanged starting material.

It would thus appear that the incorporation of a reducing agent into the alkaline reaction mixture up to the point of acidification would preclude oxidation of the intermediate dihydroquinoxalone **14** before lactam formation could occur. A medium in which all of these requirements are ideally satisfied is an alkaline solution of sodium borohydride. Indeed, treatment of an alkaline solution of the propanoic acid **3a** (R = H) with an excess of sodium borohydride at room temperature followed by acidification resulted in the separation of an essentially quantitative yield of the desired tricyclic diamide **4a** (R = H). An outstanding feature of this reaction, distinct from the ease with which it occurs, is the high degree of purity and fine crystalline form of the product. Similar treatment of the homologous acid **3b** (R = H) gave the tricyclic diamide **4b** (R = H) in almost quantitative yield. Treatment of the N-methyl derivative **3a** (R = CH_3) with sodium borohydride gave **4a** (R = CH_3).

In an attempt to delineate the scope of the sodium borohydride reductive cyclization process, attempts were made to prepare by this procedure the tricyclic derivatives **4c**, **d**, and **e** (R = H) from the corresponding carboxylic acids **3c**, **d**, and **e** (R = H). Such a route to heterocyclic systems containing medium-sized rings would have been attractive because of its synthetic simplicity, and would furthermore have made available for study an interesting series of compounds, particularly in view of the anomalous physical characteristics (ultraviolet, infrared, and n.m.r.) exhibited by many of the acid precursors and the pyrrolo[1,2-*a*]quinoxalones.[13] However, no reductive cyclization occurred with the acids **3c**, **3d**, or **3e** (R = H), which were recovered unchanged. Presumably reduction of the imine bond occurs in these cases as well, but cyclic lactam formation to the medium-sized rings is not a favored process and reoxidation to the starting quinoxalone takes precedence.

Experimental[14]

2-(2-Carboxyethyl)-3(4H)-quinoxalone (**3a**, *R = H*). A solution of 14.6 g. (0.1 mole) of α-ketoglutaric acid in 20 ml. of water was added to a solution of 10.8 g. (0.1 mole) of *o*-phenylenediamine in 100 ml. of hot water. An immediate precipitation of a colorless solid occurred. The product was collected by filtration and recrystallized from dilute acetic acid to give 20.7 g. (95%) of colorless needles, m.p. 275–277° dec. (lit.[4] m.p. 269–271° dec.).

2-Bromomethyl-4-methyl-3(4H)-quinoxalone (**5**). A solution of 14.4 g. (0.09 mole) of bromine in 30 ml. of glacial acetic acid was added dropwise to a stirred solution of 15.3 g. (0.088 mole) of 2,4-dimethyl-3(4H)-quinoxalone[15] and 7.38 g. (0.09 mole) of sodium acetate in 120 ml. of glacial acetic acid. During the addition the product began to separate as a pale yellow solid. The mixture was stirred for 4 hr. at room temperature and then filtered to gve 15.6 g. (70%) of 2-bromomethyl-4-methyl-3(4H)-quinoxalone as a pale yellow solid, m.p. 192–193° dec. The analytical sample was prepared in the form of colorless needles, m.p 193° dec., by sublimation at 170° (0.5 mm.) followed by recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_9BrN_2O$: C, 47.44; H, 3.58; N, 11.08; Br, 31.57. Found: C, 47.61; H, 3.63; N, 11.22; Br, 31.44.

(11) See J. C. E. Simpson, "The Chemistry of Heterocyclic Compounds," Vol. 5, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1953, p. 325.

(12) E. C. Taylor and M. J. Thompson, unpublished observations.

(13) We will discuss the anomalous physical characteristics of these compounds in a separate communication.

(14) Melting points were determined on a Thomas–Hoover silicone bath apparatus and are uncorrected. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Where appropriate, identity of compounds was confirmed by comparison of infrared spectra determined on a Perkin-Elmer Infracord Model 237B by the normal Nujol mull technique. All n.m.r. spectra were recorded on a Varian A-60 instrument.

(15) A. H. Cook and C. A. Perry, *J. Chem. Soc.*, 394 (1943).

2-(2,2-Dicarbethoxyethyl)-4-methyl-3(4H)-quinoxalone (**6**). 2-Bromomethyl-4-methyl-3(4H)-quinoxalone (10.12 g., 0.04 mole) was added to a solution of sodio diethyl malonate (from 6.4 g. of diethyl malonate and 0.92 g. of sodium) in 120 ml. of toluene, and the mixture was stirred and heated under reflux for 1 hr. The reaction mixture (neutral to litmus) was diluted with water, the organic layer was separated and dried over sodium sulfate, and the solvent was distilled off under reduced pressure. Trituration of the residual oil with ether gave 9.7 g. (73%) of product, m.p. 72–80°. Chromatography of a sample over alumina, with benzene as eluent, gave yellow needles, m.p. 79–83°. The melting point was raised to 86–87° by two recrystallizations from petroleum ether (b.p. 60–70°).

Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.50; H, 5.77; N, 8.46.

2-(2,2-Dicarboxyethyl)-4-methyl-3(4H)-quinoxalone. A mixture of 7.2 g. of 2-(2,2-dicarbethoxyethyl)-4-methyl-3(4H)-quinoxalone (**6**) and 50 ml. of 2 *N* sodium hydroxide was heated under reflux for 1 hr. The solution was then cooled and filtered to remove a little insoluble material, and the filtrate was treated with charcoal, filtered, and acidified. The precipitated malonic acid (4.9 g.), m.p. 172–173° dec., was recrystallized from 500 ml. of water to give 3.4 g. (57%) of pale yellow needles, m.p. 178–179° dec. The analytical sample, prepared by further recrystallization from water, melted at 179–180° dec.

Anal. Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.62; H, 4.36; N, 10.03.

2-(2-Carboxyethyl)-4-methyl-3(4H)-quinoxalone (**3a**, $R = CH_3$). *Method A.* The malonic acid prepared as described above (1.38 g.) was heated at 170–180° for 1 hr. and the cooled residue was extracted with saturated sodium bicarbonate solution. The extract was treated with charcoal and filtered, and the filtrate was acidified to give 1.03 g. (89%), which upon recrystallization from ethanol gave long, colorless needles, m.p. 180–182°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.07. Found: C, 61.87; H, 5.22; N, 11.73.

Method B. A solution of 11.8 g. (0.05 mole) of 2-(2-carboxyethyl)-3(4H)-quinoxalone in 200 ml. of water containing 11.2 g. of potassium hydroxide was treated with 12.6 g. (0.10 mole) of dimethyl sulfate, and the mixture was stirred at room temperature for 2 hr. The colorless solid obtained upon acidification with dilute sulfuric acid was recrystallized from ethanol to give 9.8 g. (84%) of colorless needles, m.p. 180–182°, identical with the product obtained by method A.

Diethyl α-ethoxalylsuccinate (**8a**)[6] was prepared in 92% yield as a pale yellow, viscous oil. Attempted distillation even under high vacuum (10^{-4} mm.) resulted in considerable decomposition, and hence the crude ester was used in all subsequent reactions. *Diethyl α-ethoxalylglutarate* (**8b**) was obtained as a pale yellow oil in 71% yield by following the prescribed procedure.[8] It could not be purified further without decomposition and hence was used crude in subsequent condensation reactions. *Diethyl α-ethoxalyladipate* (**8c**)[9] was obtained in 58% yield as a deep yellow oil which was not purified further. *Diethyl α-ethoxalylpimelate* (**8d**)[7] was prepared in 54% yield as a yellow, viscous oil.

Diethyl α-Ethoxalylsuberate (**8e**). Diethyl oxalate (14.6 g., 0.10 mole) was added to a solution of potassium ethoxide (prepared by the dropwise addition of 50 ml. of dry ethanol to 4.0 g. (0.10 mole) of potassium metal in 75 ml. of anhydrous ether) and the pale yellow solution was allowed to stand at room temperature for 15 min. Diethyl suberate (23.0 g., 0.10 mole) was added all at once and the yellow mixture allowed to stand at room temperature for 5 days. The mixture was poured into 100 ml. of 20% sulfuric acid containing an equal volume of ice and the cold, acidic solution was extracted with ether (five 100-ml. portions). The combined ethereal extracts were then extracted with 20% (w./v.) aqueous potassium carbonate solution (five 50-ml. portions). The combined alkaline extracts were acidified with concentrated hydrochloric acid, the stirred mixture being kept cool by addition of ice. The yellow oil which separated was extracted with ether (five 100-ml. portions) and the combined ether extracts were dried ($MgSO_4$). Removal of the solvent by evaporation *in vacuo* gave 17.2 g. (56%) of a viscous yellow oil whch could not be purified further.

Diethyl α-(2(1H)-oxo-3-quinoxalyl)suberate (**10e**). A solution of 2.16 g. (0.02 mole) of *o*-phenylenediamine and 6.12 g. (0.02 mole) of diethyl α-ethoxalylsuberate in 50 ml. of ethanol was allowed to stand at room temperature for 18 hr. The mixture was filtered to remove a yellow solid (1.63 g.), the filtrate was diluted with 1 l. of water, and the yellow suspension was extracted with ether (three 150-ml. portions). The combined ethereal extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow viscous oil which solidified on cooling to a semisolid mass, m.p. 70–105°. This solid was dissolved in ether and passed through a column of 120 g. of acid-washed Merck alumina. The first 25 ml. of eluate (bright yellow in color) was discarded and the product then washed off the column with an additional 600 ml. of ether. Evaporation to dryness gave 3.42 g. (46%) of a pale yellow solid, m.p. 85–90°. The analytical sample, m.p. 90–92°, was prepared by repeated crystallization from *n*-hexane.

Hydrolysis of the Diesters **10a–e**. *Formation of the Acids* **3a–e** ($R = H$). The following general procedure was used for the preparation of all of the acids **3a–e** (R = H). A solution of the diester (10.0 g.) in 25 ml. of ethanol was added to a solution of 10.0 g. of potassium hydroxide in 15 ml. of water, the mixture was heated under reflux for 4 hr., treated with charcoal, and filtered, and the filtrate was acidified. The precipitated acid was collected by filtration and recrystallized from the appropriate solvent. See Table I.

2-(3-Carboxypropyl)-4-methyl-3(4H)-quinoxalone (**3b**, $R = CH_3$) was prepared in 92% yield from 2-(3-carboxypropyl)-3(4H)-quinoxalone (**3b**, R = H) by treatment with dimethyl sulfate and potassium hydroxide, as described above for the preparation of **3a** ($R = CH_3$). The product was recrystallized from hot water as long, glistening colorless needles, m.p. 147–150°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.28; H, 5.60; N, 11.50.

1,2,3-Cyclohexanetrione 1,3-dioxime (**11**) was best prepared according to the procedure of Treibs and Kuhn[10a]

Table I

Quinoxalone diester	Recrystallization solvent	Yield, %	Physical form	M.p., °C.	Formula	Anal. Calcd., % C	H	N	Found, % C	H	N
10a	50% aq. C_2H_5OH	91	Colorless needles	112–114	$C_{16}H_{18}N_2O_5$	60.37	5.70	8.80	59.91	5.71	8.96
10b	Ethyl acetate–petroleum ether[a]	89	Colorless needles	130–132	$C_{17}H_{20}N_2O_5$	61.43	6.07	8.43	61.50	6.17	8.46
10c	Benzene–petroleum ether[a]	93	Pale pink needles	104–105.5	$C_{18}H_{22}N_2O_5$	62.41	6.40	8.09	62.48	6.52	8.16
10d	Ethyl acetate–petroleum ether[a]	84	Pale yellow needles	72–74	$C_{19}H_{24}N_2O_5$	63.32	6.71	7.77	63.46	6.75	7.95
10e	*n*-Hexane	46	Colorless needles	90–92	$C_{20}H_{26}N_2O_5$	64.15	7.00	7.48	64.30	7.18	7.28

[a] B.p. 60–70°.

Table II

Quinoxalone acid[a]	Recrystallization solvent	Yield, %	Physical form	M.p., °C.	Formula	Anal. Calcd., % C	H	N	Found, % C	H	N
3a	Acetic acid	90	Colorless needles	275–277 dec.	$C_{11}H_{10}N_2O_3$	60.54	4.62	12.84	60.60	5.07	13.41
3b	50% aq. C_2H_5OH	83	Colorless needles	216–218	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	61.96	5.29	12.26
3c	25% aq. C_2H_5OH[b]	87	Pale pink needles	179–180.5	$C_{14}H_{14}N_2O_3$	63.40	5.73	11.38	63.23	5.93	11.25
3d	50% aq. C_2H_5OH	98	Fawn colored needles	210–213	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76	64.48	6.26	10.66
3e	C_2H_5OH	98	Pale yellow needles	150–153	$C_{15}H_{18}N_2O_3$	65.67	6.61	10.21	65.65	6.77	10:36

[a] R = H. [b] 25:75 (v./v.).

and was obtained in 76% yield as yellow needles, m.p. 220–223° dec. (lit.[10a] m.p. 223° dec.). An alternative procedure[10b] gave a somewhat higher yield (85%) of the dioxime, but in this case it was obtained as a brown powder of lower melting point (210–220° dec.).

Ethyl 5-cyano-2-oximinopentanoate (**12**), prepared in 81% yield according to the published procedure,[10b] was best purified by distillation (b.p. 170–175° at 0.2 mm.) followed by crystallization from carbon tetrachloride. It was obtained as colorless, chunky crystals, m.p. 67–71° (lit.[16] m.p. 74°).

2-(3-Cyanopropyl)-3(4H)-quinoxalone (**13**). A solution of 1.08 g. (0.01 mole) of *o*-phenylenediamine in 5 ml. of hot water was added to a solution of 1.84 g. (0.01 mole) of 5-cyano-2-oximinopentanoate in 20 ml. of water containing 0.2 ml. of acetic acid, and the mixture was heated at 50° for 20 min. It was then allowed to stand at room temperature for 6 hr., heated to reflux, treated with charcoal, and filtered, and the filtrate was chilled to 0°. The precipitated solid was collected by filtration to give 2.05 g. (96%) of fawn-colored needles, m.p. 199–201° dec. Recrystallization from 50% aqueous ethanol gave long, colorless needles, m.p. 200–201° dec.

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.32; H, 5.22; N, 19.67.

2-(3-Carboxypropyl)-3(4H)-quinoxalone (**3b**, *R = H*). The above cyano compound was heated under reflux for 18 hr. with 4 *N* sodium hydroxide solution. Decolorization with charcoal followed by acidification gave 2-(3-carboxypropyl)-3(4H)-quinoxalone (**3b**, R = H) in 89% yield as colorless needles, m.p. 215–218° (see Table II).

1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoxalin-1,4-dione (**4a** *R = H*). *Method A. Raney Nickel in Sodium Hydroxide.* A solution of 2.0 g. of 2-(2-carboxyethyl)-3(4H)-quinoxalone (**3a**, R = H) in 25 ml. of 1 *N* sodium hydroxide solution was shaken at room temperature for 4 hr. with 2 g. of Raney nickel[17] under 40 p.s.i. of hydrogen. The catalyst was filtered off, the alkaline solution was acidified, and the colorless precipitate was collected by filtration to give 1.7 g. of crude product. The infrared spectrum of this material showed the presence of unchanged carboxylic acid (ν_{O-H} 3300–2900 cm.$^{-1}$; $\nu_{C=O}$ 1695 cm.$^{-1}$), which was removed by boiling the product in 50% aqueous ethanol and filtering to remove the unchanged starting material. Evaporation of the ethanol filtrate and recrystallization of the residue from 50% aqueous ethanol gave 0.97 g. (49%) of the tricyclic product **4a** (R = H) as colorless needles, m.p. 238–240°.

Method B. Raney Nickel in Acetic Anhydride. A solution of 2.0 g. of the acid (**3a**, R = H) in 25 ml. of acetic anhydride was hydrogenated as described above. Removal of the solvent by distillation under reduced pressure left a semisolid, pale yellow gum whose infrared spectrum showed the presence of unchanged starting material. Sublimation of this crude product at 150° (0.1 mm.) gave 1.18 g. (58%) of a colorless

(16) E. Fischer and F. Weigert, *Chem. Ber.*, **35**, 3772 (1902).

(17) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

solid, m.p. 210–217°. Two recrystallizations from 50% aqueous ethanol raised the melting point to 236–239°.

Method C. Raney Nickel in Acetic Acid. Hydrogenation of **3a** (R = H) in acetic acid, as described above, followed by removal of the solvent under reduced pressure, gave a yellow gum which was sublimed at 150° (0.1 mm.). Recrystallization of the sublimate from 50% aqueous ethanol gave **4a** (R = H), m.p. 238–240°, in 69% yield.

Method D. Raney Nickel in Ethanol. Hydrogenation of **3a** (R = H) in ethanol, as described above, followed by removal of the solvent under reduced pressure, gave a pale yellow, semisolid mass. This was stirred with acetic anhydride overnight, the solvent was removed under reduced pressure, and the residual gum was sublimed at 150° (0.1 mm.). Recrystallization of the resulting colorless sublimate from 50% aqueous ethanol gave **4a** (R = H), m.p. 237–240°, in 61% yield.

Method E. Zinc in Acetic Acid. A mixture of 1.0 g. of 2-(2-carboxyethyl)-3(4H)-quinoxalone and 2 g. of zinc dust was stirred in 50 ml. of acetic acid at room temperature for 2 hr. The solid material was filtered off and the acid was removed by distillation under reduced pressure. The residual pale yellow oil and the solids which had been collected by filtration were refluxed for 1 hr. with 50 ml. of acetic anhydride, the hot reaction mixture was filtered free of zinc and zinc acetate, the solvent was distilled off under reduced pressure, and the residual gummy solid was sublimed at 150° (0.1 mm.). The resulting colorless solid (0.5 g., 49%) was recrystallized from 50% aqueous ethanol to give colorless needles, m.p. 235–240°.

Method F. Sodium Borohydride in Sodium Hydroxide. Sodium borohydride (1.0 g.) was added to a solution of 2.0 g. of 2-(2-carboxyethyl)-3(4H)-quinoxalone in 20 ml. of 1 *N* sodium hydroxide and the mixture was allowed to stand at room temperature for 6 hr. Acidification with 6 *N* sulfuric acid gave a clear solution from which the product crystallized as beautiful colorless needles (1.92 g., 98%), m.p. 237–240°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.48; H, 5.07; N, 13.71.

The products obtained by methods A–F were identical, as judged by a comparison of infrared spectra and by mixture melting point determinations.

1,2,3,3a,4,5-Hexahydro-5-methylpyrrolo[1,2-a]quinoxaline-1,4-dione (**4a**, *R* = CH_3). A solution of 2.0 g. of 2-(2-carboxyethyl)-4-methyl-3(4H)-quinoxalone and 1 g. of sodium borohydride in 20 ml. of 1 *N* sodium hydroxide was allowed to stand at room temperature for 6 hr. and then acidified with 6 *N* sulfuric acid. The resulting clear solution deposited 1.88 g. (93%) of beautiful, colorless needles, m.p. 164–168°, upon standing for 1 hr. Recrystallization from aqueous ethanol raised the melting point to 167–169.5°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.52; H, 5.73; N, 13.29.

1,2,3,4,4a,5,6-Heptahydropyridino[1,2-a]quinoxaline-1,5-dione (**4b**, *R* = *H*) was obtained in 78% yield by treatment of 2-(3-carboxypropyl)-3(4H)-quinoxalone (**3b**, R = H) with sodium borohydride as described above. The product crystallized from 50% aqueous ethanol as beautiful, long colorless needles, m.p. 235–237°

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.83; H, 5.67; N, 12.96.

Synthesis of Pyrrolo[2,3-*d*]pyrimidines. The Aglycone of Toyocamycin[1,2]

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4-Amino-5-cyanopyrrolo[2,3-d]pyrimidine (**2b**), *the aglycone of the antibiotic Toyocamycin, has been prepared from tetracyanoethylene in five steps by reaction with hydrogen sulfide to give 2,5-diamino-3,4-dicyanothiophene* (**4**), *rearrangement with alkali to 2-mercapto-3,4-dicyano-5-aminopyrrole* (**5**), *reaction with trimethyl orthoformate to the methoxymethyleneamino derivative* **6b**, *cyclization with ammonia to 4-amino-5-cyano-6-methylmercaptopyrrolo[2,3-d]pyrimidine* (**8b**), *and finally desulfurization with Raney nickel. 4-Aminopyrrolo[2,3-d]pyrimidine* (**1b**), *the aglycone of the antibiotic Tubercidin, has been prepared from* **2b** *by acid hydrolysis of the cyano grouping to the corresponding 5-carboxylic acid* **11b**, *followed by decarboxylation. Ribosidation of the aglycone* **2b** *via its chloromercury salt gave what is believed to be the 1-ribosyl derivative rather than Toyocamycin itself (the 7-ribosyl derivative). A number of structural analogs of the aglycones* (**1b** *and* **2b**) *of Tubericidin and Toyocamycin, differing from the natural products in possessing a substituted 4-amino group, or alkyl or aryl groups in position 5, were prepared from the 2-amino-3-cyano-4-substituted pyrroles* **15** *and* **16** *by reaction with triethyl orthoformate to give the 2-ethoxymethylenamino derivatives* **17** *and* **18**, *conversion to the formamidines* **19–23** *with amines, cyclization to pyrrolo[2,3-d]pyrimidines* **24–28** *with sodium methoxide in methanol, and rearrangement of the 3-substituted 4-imino derivatives* **26–28** *with boiling water to their aromatic isomers* **29–31**.

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(2) A preliminary report of this work has appeared; E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **86**, 951 (1964).

(3) National Institutes of Health Predoctoral Fellow, 1961–1964.