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

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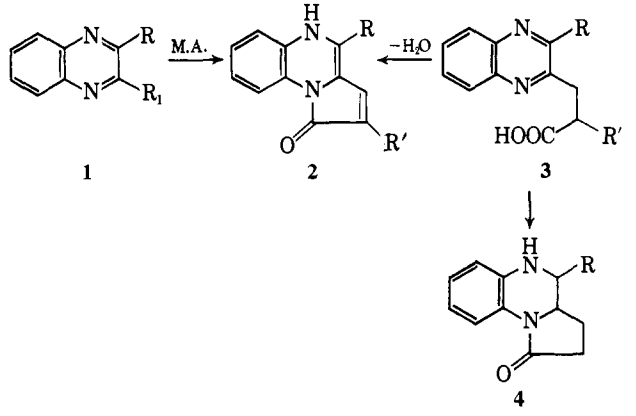
A convenient and simple preparative route to the tricyclic amides (**4a, b,** *and* **c**) *has been found in the reductive cyclization of β-quinoxalinylpropenoic* (**5a, b,** *and* **c**) *and -propanoic* (**3a, b,** *and* **c**) *acids with hydrogen and Raney nickel. A number of alternative synthetic routes to the former intermediates were developed; in particular, β-quinoxalinylpropenoic acid itself* (**5c**) *was prepared by three different routes in order to clarify certain discrepancies in its reported properties. The propanoic acid intermediates* (**3a, b,** *and* **c**) *were prepared both by cautious reduction of the corresponding propenoic acids and by direct synthesis from o-phenylenediamine and γ-oximino-γ-acetyl- and γ-oximino-γ-benzoylbutanoic acid. Syntheses of the latter compounds are also described.*

Previous work in this laboratory has shown that reaction of various 2,3-disubstituted quinoxalines (**1a** and **b**) with maleic anhydride (M.A.) leads to the virtually unknown tricyclic pyrrolo[1,2-*a*]quinoxaline system (**2a** and **b**) rather than to the "Diels–Alder adducts" originally claimed.[2] This novel entry into the 1,4-dihydroquinoxaline ring system has prompted additional synthetic work in this area, and during the latter part of these earlier studies it was found that the tricyclic compounds (**2c, d,** and **e**) could readily be prepared by cyclodehydration of substituted β-quinoxalinylpropanoic acids (**3a, b,** and **d**).[3] We were intrigued



1a, R = R_1 = CH_3
b, R = C_6H_5; R_1 = CH_3
c, R = H; R_1 = CH_3

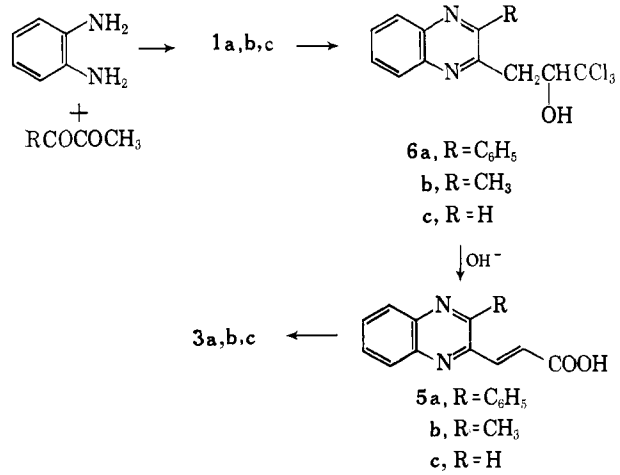
2a, R = CH_3; R′ = CH_2COOH
b, R = C_6H_5; R′ = CH_2COOH
c, R = C_6H_5; R′ = CH_3
d, R = C_6H_5; R′ = H
e, R = CH_3; R′ = H

3a, R = C_6H_5; R′ = H
b, R = CH_3; R′ = H
c, R = R′ = H
d, R = C_6H_5; R′ = CH_3

4a, R = C_6H_5
b, R = CH_3
c, R = H

by the possibility that application of these synthetic routes to other condensed pyrazine heterocycles might provide a simple and unequivocal entry into such difficultly accessible structural types as 5,6-dihydropteridines, which are known to be of considerable importance in biological systems. Accordingly, synthetic work in the pyrrolo[1,2-*a*]quinoxaline system has been extended and a reinvestigation of methods for the preparation of the requisite substituted propanoic acids (**3a, b,** and **c**) has been carried out. This paper describes improved syntheses of β-2-quinoxalinylpropanoic acid (**3c**) itself, new synthetic methods for the preparation of β-3-phenyl- (**3a**) and β-3-methyl-2-quinoxalinylpropanoic acids (**3b**), and a remarkably facile reductive cyclization of these β-quinoxalinylpropanoic acids in the presence of Raney nickel to give derivatives of the hexahydropyrrolo[1,2-*a*]quinoxaline system (**4a, b,** and **c**). We consider this latter reductive cyclization of considerable potential synthetic utility because of the mildness of the conditions employed and the high yields obtained. To our knowledge few examples of reductive cyclization of comparable systems have been reported and in no instance does cyclization occur under such mild conditions as are reported here.[4]

The propenoic acids (**5a, b,** and **c**) were prepared by modifications (see Experimental) of the well known but generally unsatisfactory chloral method of chain extension, starting with the methylquinoxaline derivatives (**1a, b,** and **c**). Subsequent reduction under carefully controlled conditions gave the desired propanoic acids (**3a, b,** and **c**). This sequence of reactions was not satisfactory for large-scale preparations, however, because of difficulties encountered in the purification and reduction of the highly insoluble propenoic acids. We were thus led to an investigation of alternate preparations of the propanoic acids (**3a, b,** and **c**) with the results described below.

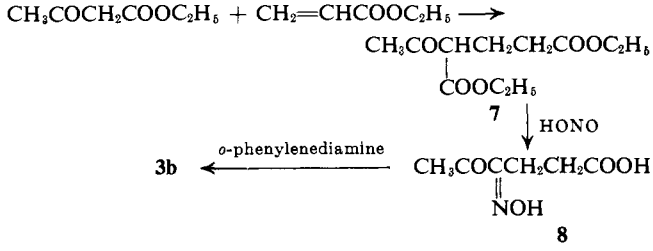


6a, R = C_6H_5
b, R = CH_3
c, R = H

5a, R = C_6H_5
b, R = CH_3
c, R = H

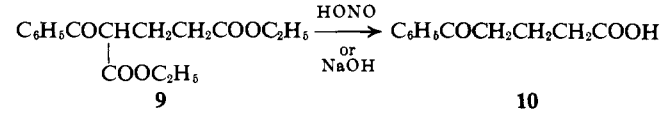
(1) This work was supported in part by a grant to Princeton University from the American Cancer Society.
(2) E. C. Taylor and E. S. Hand, *J. Am. Chem. Soc.*, **85**, 770 (1963).
(3) E. C. Taylor and G. W. H. Cheeseman, *ibid.*, **86**, 1830 (1964).
(4) (a) V. Boekelheide and E. J. Agnello, *ibid.*, 72, 5005 (1950); (b) C. W. Tullock and S. M. McElvain, *ibid.*, 61, 961 (1939); (c) M. G. Reinecke and L. R. Kray, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964 p. 5M; *J. Org. Chem.*, **29**, 1736 (1964).

β-3-Methyl-2-quinoxalinylpropanoic Acid (**3b**). If this 2,3-disubstituted quinoxaline were to be prepared by the classical quinoxaline synthesis from *o*-phenylenediamine and an α-dicarbonyl compound, one would require, as the aliphatic precursor, γ-keto-γ-acetylbutanoic acid. This is not, however, a known compound despite its apparent simplicity of structure. However, an alternative route to quinoxalines from *o*-phenylenediamine can involve other mono- or difunctional derivatives of α-diketones, including α-oximino ketones.[5] γ-Oximino-γ-acetylbutanoic acid (**8**) was prepared by condensation of ethyl acrylate with ethyl acetoacetate under modified Michael conditions to give diethyl α-acetylglutarate (**7**),[6] which upon



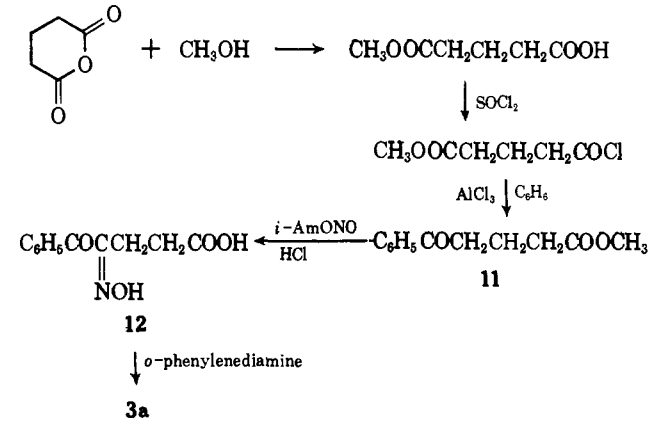
subsequent treatment with nitrous acid underwent hydrolysis of the ester groupings and decarboxylation of the resulting β-keto acid, with concomitant nitrosation of the active methylene grouping α to the ketone.[7] Condensation of **8** with *o*-phenylenediamine gave β-3-methyl-2-quinoxalinylpropanoic acid (**3b**) in excellent yield (80–90%).

β-3-Phenyl-2-quinoxalinylpropanoic Acid (**3a**). Condensation of ethyl benzoylacetate under modified Michael conditions[6] with ethyl acrylate gave diethyl α-benzoylglutarate (**9**) in high yield (97%). The use of sodium ethoxide rather than Triton B[8] represents a significant improvement over the only previously published description of this reaction. Treatment of the diester **9** with nitrous acid in the cold resulted in hydrolysis of the ester groupings and consequent decarboxylation to give γ-benzoylbutanoic acid (**10**),[9] but surprisingly no oximination of the active methylene group was observed.[10] Although other methods (*i.e.*,



the use of aliphatic nitrites) could have been used in attempts to effect this recalcitrant nitrosation, this synthetic route possessed the inherent disadvantage that separation of the oxime, if formed, from unchanged acid would be difficult because of the solubility of both in alkali. Use of the corresponding ester **11**, which would obviate this difficulty, is itself complicated by the probability that facile lactonization would result from attempted esterification of the acid **10**. Thus an alternative route to the desired ester **11** was sought.

Methanolysis of glutaric anhydride[11] gave γ-carbomethoxybutanoic acid which, on conversion to the acid chloride and treatment with benzene in the presence of aluminum chloride, gave methyl γ-benzoylbutanoate (**11**) in an over-all yield of 62%. Treatment of a



solution of this ester in ether with concentrated hydrochloric acid and isoamyl nitrite resulted both in nitrosation of the active methylene group and hydrolysis of the methyl ester to furnish γ-oximino-γ-benzoylbutanoic acid (**12**) directly in almost quantitative yield. Condensation of this intermediate with *o*-phenylenediamine yielded the desired β-3-phenyl-2-quinoxalinylpropanoic acid (**3a**) in excellent (80–90%) yield.

β-2-Quinoxalinylpropanoic Acid (**3c**). A number of procedures for the preparation of this compound have been described[2,3,12] and of these, the route *via* the chloral adduct derived from 2-methylquinoxaline appears to be the method of choice. Possible alternative syntheses of **3c** were investigated but were unsuccessful. One of the more promising possible alternatives was prompted by a recently published synthesis of α-keto aldehydes (monosubstituted glyoxals) by chain extension of acid chlorides through reaction with diazomethane to give the diazo ketone, conversion with triphenylphosphine to the glyoxal-1-triphenylphosphazine, and subsequent decomposition of the latter

(5) Condensation of α-oximino ketones with *o*-phenylenediamine to give quinoxalines has been described by S. Gabriel and A. Sonn, *Chem. Ber.*, **40**, 4850 (1907); O. Fischer and F. Römer, *ibid.*, **41**, 2350 (1908); K. A. Böttcher, *ibid.*, **46**, 3084 (1913). Condensation of *o*-phenylenediamine with an α-dioxime is reported by E. Durio, *Gazz. chim. ital.*, **63**, 747 (1933).

(6) H. Henecka, *Chem. Ber.*, **81**, 197 (1948); H. Kappeler, D. Stauffacher, A. Eschenmoser, and H. Schinz, *Helv. Chim. Acta*, **37**, 957 (1954).

(7) G. Baldraco, *J. prakt. Chem.*, [2] **49**, 197 (1894).

(8) G. N. Walker, *J. Am. Chem. Soc.*, 77, 3664 (1955).

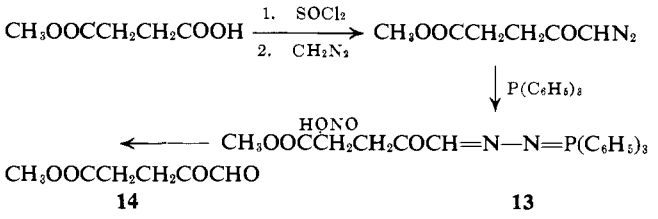
(9) γ-Benzoylbutanoic acid (**10**) has been previously prepared in 85–90% yield by a Friedel–Crafts reaction of benzene with glutaric anhydride: "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 82. Glutaric anhydride, however, is an expensive reagent, and it is felt that the above synthesis of **10** represents an attractive alternative, particularly since hydrolysis of the ester **9** with base, with concomitant decarboxylation, proceeds in virtually quantitative yield to give the free acid **10**. The difficult accessibility of this acid is reflected by the fact that only its ethyl ester, prepared by treatment of the silver salt of the acid with ethyl iodide, has been reported: J. Wislicenus and C. K. Kuhn, *Ann.*, **302**, 220 (1898). It is, however, interesting to note that a recent publication demonstrates its potential utility by its straightforward conversion to 6-phenyl-α-pyrone: M. Yu. Lur'e, I. S. Trubnikov, N. P. Shusherina, and L. Ya. Levine, *Zh. Obshch. Khim.*, **28**, 135 (1958). Since this latter compound should be capable of conversion to 6-phenyl-2-pyridone by treatment with ammonia, and variously substituted benzoylacetic esters and -acrylic esters (precursors for variously substituted derivatives of **10**) are readily available, the above-described synthesis of γ-benzoylbutanoic acid should serve as a model for the preparation of substituted derivatives capable of conversion into otherwise difficultly accessible heterocycles.

(10) There are apparently no reported instances of oximination of alkyl aryl ketones of the type $ArCOCH_2R$ with nitrous acid: O. Touster, *Org. Reactions*, 7, 327 (1953). Subsequent efforts to nitrosate γ-benzoylbutanoic acid (**10**) were also unsuccessful.

(11) S. A. Harris, D. E. Wolf, R. Mozingo, G. E. Arth, R. C. Anderson, N. R. Easton, and K. Folkers, *J. Am. Chem. Soc.*, 67, 2096 (1945).

(12) (a) W. Reid and H. Keller, *Chem. Ber.*, **89**, 2580 (1956); (b) R. G. Jones, E. C. Kornfeld, and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950); (c) A. S. Elina, *Zh. Obshch. Khim.*, **29**, 2763 (1959).

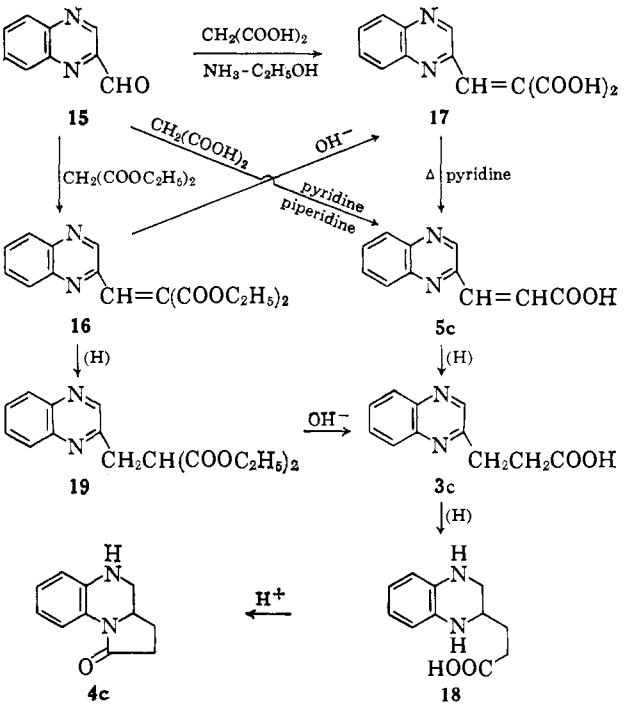
intermediate with nitrous acid.[13] An attempt was made to adapt this promising method to the synthesis of our required glyoxal **14**. Thus, β-carbomethoxypropanoic acid, prepared by methanolysis of succinic anhydride, was treated with thionyl chloride to give the acid chloride,[14] then with diazomethane to give the diazo ketone, and finally with triphenylphosphine to give the beautifully crystalline, bright yellow triphenylphosphazine derivative **13**. We were able to convert this readily



14 **13**

accessible derivative to the desired glyoxal **14** as demonstrated by its isolation as a bis-2,4-dinitrophenylhydrazone. However, all attempts to condense this glyoxal with *o*-phenylenediamine were unsuccessful.

Our initial incentive to search for possible alternative synthetic routes to β-2-quinoxalinylpropanoic acid (**3c**) arose from difficulties encountered in handling and characterizing the propenoic acid intermediate **5c**, formed by basic hydrolysis and dehydration of the chloral adduct (**6c**) of 2-methylquinoxaline. Rigorous purification of our propenoic acid **5c** resulted in a product which melted 23° higher than previously reported and which differed also in physical properties (color and solubility). We therefore undertook an independent, unequivocal preparation of the propenoic acid **5c** in order to confirm the course of the chloral condensation and hydrolysis sequence, since Woodward and Kornfeld have demonstrated that in one instance, at least, the addition of chloral to an active methyl group followed by hydrolysis leads to an anomalous product.[15] Oxidation of 2-methylquinoxaline with selenium dioxide[16] gave the corresponding 2-aldehyde **15** which was condensed with malonic ester to give the diester **16**. Hydrolysis of this diester **16** gave the diacid **17** which upon decarboxylation yielded the propenoic acid **5c**, identical in every respect with the product obtained by the chloral sequence. Furthermore, direct condensation of aldehyde **15** with malonic acid in pyridine solution containing piperidine gave the same propenoic acid **5c** in one step.[17] Condensation of the aldehyde **15** with malonic acid in ethanolic ammonia[18] yielded the diacid **17**, identical with the product obtained by hydrolysis of the diester. Finally, reduction of the diester **16** with hydrogen in the presence of palladium-on-charcoal catalyst to give the diester **19**, followed by hydrolysis and decarboxylation,[12c] gave β-2-quinoxalinylpropanoic acid (**3c**) identical with the material prepared by reduction under the same conditions of the propenoic acid **5c**. We thus consider



the structure of the propenoic acid **5c** firmly established.

Reductive Cyclization. We were surprised to find that attempted repetition of the previously described reduction of the propenoic acid **5c** to the propanoic acid **3c** with hydrogen and Raney nickel in alkaline solution, followed by acidification to precipitate the free propanoic acid, never led to the expected product.[12a,b] In contrast to the literature descriptions of this reaction, acidification of the reduction mixture did not lead to precipitation, but gave a clear solution which gradually darkened upon standing. Readjustment of the solution to alkalinity, however, discharged the color and resulted in the instantaneous separation of a colorless, basic, crystalline solid. Microanalysis indicated the empirical formula $C_{11}H_{12}N_2O$ which differed from the expected propanoic acid **3c** by the loss of the elements of water. Its infrared spectrum showed the total absence of any bands normally characteristic of a carboxylic acid group, but showed a strong carbonyl absorption band at 1670 cm.$^{-1}$ and a strong, sharp N–H band at 3295 cm.$^{-1}$. The product formed a mono-N-acetyl derivative, and thus appeared to be the tricyclic hexahydropyrrolo[1,2-*a*]quinoxaline **4c**. This structural assignment was rigorously confirmed by examination of its n.m.r. spectrum in trifluoroacetic acid, which indicated three aromatic protons as a singlet with some side band splitting at 428 c.p.s. (7.14 p.p.m.) and one aromatic proton as a well resolved doublet at 503 and 509 c.p.s. The alicyclic protons gave a series of bands with multiple splitting in the range 147–245 c.p.s. It is thus clear that the expected propanoic acid **3c** had been further reduced to the tetrahydroquinoxaline **18**, which then lactamized upon acidification.

The efficacy of the above reductive cyclization appears to be directly proportional to the amount of Raney nickel catalyst employed. The previously observed reduction of the propenoic acid **5c** only to the propanoic acid **3c** must reflect the use of a very small quantity of Raney nickel by previous investigators,[12a,b] although

(13) H. J. Bestmann, O. Klein, V. Göthlich and H. Buckschewski, *Chem. Ber.*, 96, 2259 (1963).
(14) J. Cason, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 169.
(15) R. B. Woodward and E. C. Kornfeld, *J. Am. Chem. Soc.*, 70, 2508 (1948).
(16) J. K. Landquist and J. A. Silk, *J. Chem. Soc.*, 2052 (1956).
(17) R. D. Haworth, W. H. Perkin, and J. Rankin, *ibid.*, 1693 (1924); R. D. Haworth, W. H. Perkin, and H. S. Pink, *ibid.*, 1714 (1925).
(18) E. Knoevenagel, *Chem. Ber.*, **31**, 2605 (1898).

even in our hands a mixture of the propanoic acid **3c** and the reductive cyclization product **4c** was inevitably obtained. Exclusive formation of the pyrroloquinoxaline **4c**, uncontaminated by either unchanged starting material or propanoic acid **3c**, was achieved by the use of equal weights of Raney nickel and the propenoic acid. We have no explanation for this remarkable dependence of the reduction upon such extraordinary quantities of Raney nickel. It should be pointed out, however, that exclusive reduction of the propenoic acid **5c** to the propanoic acid **3c** can be achieved by the use of palladium-on-carbon catalyst (rather than Raney nickel) in dilute sodium hydroxide solution at atmospheric pressure of hydrogen.

That the unsaturated side chain is not a prerequisite for reductive cyclization (*i.e.*, that reduction of the ring and cyclization does not precede reduction of the α,β-unsaturated carbonyl system) was clearly indicated by the observation that the propanoic acid **3c** was likewise converted upon Raney nickel reduction to the same hexahydropyrrolo[1,2-*a*]quinoxaline **4c**.

In analogous fashion, the 3-phenyl- (**3a**) and 3-methyl-β-2-quinoxalinylpropanoic acids (**3b**) were reductively cyclized with hydrogen and Raney nickel to give the corresponding tricyclic derivatives **4a** and **4b**. It should be noted that these hexahydropyrrolo[1,2-*a*]-quinoxalines are not accessible by reduction of the pseudo "Diels–Alder adducts."[2,3] Derivatives of the reduced pyrrolo[1,2-*a*]quinoxaline system may, therefore, be more readily accessible by reductive cyclization as described herein, and efforts directed toward extending these observations are under way.

Experimental[19]

2,3-Dimethyl-,[20] *-2-methyl-3-phenyl-*,[3] *and 2-methylquinoxaline*[12b] (**1a**, **b**, *and* **c**) were prepared by condensation of pure, recrystallized *o*-phenylenediamine with butane-2,3-dione, 1-phenylpropane-1,2-dione, and glyoxal, respectively. 2,3-Dimethylquinoxaline was purified by recrystallization from water and melted at 104–106° (lit.[20] m.p. 104–106°). 2-Methyl-3-phenylquinoxaline was purified by sublimation at 50°(0.5 mm.) and melted at 56–58° (lit.[3] m.p. 57–58°). 2-Methylquinoxaline was always freshly distilled before use[21]; b.p. 121–122° (15 mm.) (lit.[12b] b.p.125–127° (11 mm.)).

α,α,α-Trichloro-β-hydroxy-γ-2-quinoxalinylpropane (**6c**) was prepared by the following modification of the literature procedures.[12a,b] A mixture of 2-methylquinoxaline (14.4 g.), chloral (18.5 g.), and pyridine (1 ml.) was heated at 80° for 1 hr. The cooled reaction mixture was diluted with water and the oil which precipitated was extracted with ether. The ethereal extract was washed successively with water, dilute sodium bicarbonate solution, water, dilute hydrochloric acid, and water, and was then dried ($MgSO_4$). Removal of the solvent and trituration of the resulting pink oil with petroleum ether (b.p. 60–70°) gave a pale pink solid (~21 g.), m.p. 100–106°. Recrystallization twice from petroleum ether (b.p. 60–70°) gave 19.6 g. (67%) of α,α,α-trichloro-β-hydroxy-γ-2-quinoxalinylpropane as beautiful, chunky, pale pink crystals, m.p. 104–107° (lit.[12a] m.p. 106°).

β-2-Quinoxalinylpropenoic Acid (**5c**). *Method A.* To a solution of the chloral adduct **6c** (24 g.) in 100 ml. of ethanol was added 35 ml. of 12.5 *N* sodium hydroxide. The mixture was heated carefully on a water bath to 60–70°, when a vigorous reaction ensued. When this reaction had subsided, 750 ml. of water was added to the dark brown reaction mixture, the resulting solution was treated with charcoal, and the filtrate was acidified. This gave a brown powder (~20 g.) which was recrystallized from a large volume of ethanol to give 12.8 g. (67%) of β-quinoxalinylpropenoic acid as a tan powder, m.p. 239–243° dec. (lit.[12a] m.p. 219–220°). Further crystallization from ethanol gave the product as fawn-colored needles, m.p. 240–243° dec. (see below for methods B and C).

β-3-Phenyl-2-quinoxalinylpropenoic Acid (**5a**). Condensation of 2-methyl-3-phenylquinoxaline (**1b**) with chloral exactly as described for 2-methylquinoxaline gave the required chloral adduct (80%) as a pink oil which slowly solidified on standing. Treatment of this adduct with base then gave a 52% yield of β-3-phenyl-2-quinoxalinylpropenoic acid as a brown solid, m.p. 255–258° dec. (lit.[3] m.p. 256–257°).

β-3-Methyl-2-quinoxalinylpropenoic acid (**5b**) was prepared in 37% over-all yield by the same procedure as described for the propenoic acids **5a** and **5c**. It was obtained as fawn colored needles, m.p. 210–212° (lit.[2] m.p. 213°), by repeated crystallization from a large volume of ethanol.

Reduction of the Propenoic Acids **5a, b** *and* **c** *to the Propanoic Acids* **3a, b**, *and* **c**. A solution of the propenoic acid (2.0 g.) in 1 *N* sodium hydroxide (25 ml.) was stirred under hydrogen at atmospheric pressure with 10% palladium-on-charcoal (0.5 g.) as catalyst. The calculated amount of hydrogen was absorbed in about 1.5 hr. Removal of the catalyst and acidification precipitated the propanoic acid as a pale brown solid.

β-3-Phenyl-2-quinoxalinylpropanoic acid (**3a**) was obtained in 50–60% yield, and crystallization of the crude product from 10% aqueous ethanol gave the product as colorless needles, m.p. 150–152° (lit.[3] m.p. 162–163°).

β-3-Methyl-2-quinoxalinylpropanoic acid (**3b**), obtained in 50–60% yield, crystallized from a large volume of water as colorless needles, m.p. 165–167° (lit.[2] m.p. 167–168°).

β-2-Quinoxalinylpropanoic acid (**3c**) was obtained in 40–65% yield and was best purified by slow sublimation at 100° (0.1 mm.) to give a colorless solid, m.p. 112–113° (lit.[12b] m.p. 116°).

Diethyl α-Acetylglutarate (**7**) was obtained in 77% yield as a colorless oil, b.p. 92–94° (0.05 mm.) (lit.[6] b.p. 110–112° (0.1 mm.)).

γ-Oximino-γ-acetylbutanoic Acid (**8**). Treatment of diethyl α-acetylglutarate with nitrous acid according to the literature procedure[7] gave yields of 40–60% of γ-

(19) Melting points were determined on a Thomas–Hoover silicon bath apparatus and are uncorrected. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich., and the Robertson Microanalytical Laboratory, Florham Park, N. J. 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 the n.m.r. spectra were recorded on a Varian A-60.

(20) R. W. Bost and E. E. Towell, *J. Am. Chem. Soc.*, 70, 903 (1948).

(21) Freshly distilled 2-methylquinoxaline, which is a colorless, mobile oil, rapidly turns deep red in color, even when stored in the dark at 0°. This deep red color is due to formation of "2-methylquinoxaline orange"; C. L. Leese and H. N. Rydon, *J. Chem. Soc.*, 303 (1955).

oximino-γ-acetylbutanoic acid, m.p. 90–93° (lit.[7] m.p. 97–97.5°).

β-3-Methyl-2-quinoxalinylpropanoic Acid (**3b**). γ-Oximino-γ-acetylbutanoic acid (15.9 g., 0.10 mole) was added to a solution of freshly crystallized *o*-phenylenediamine (10.8 g., 0.10 mole) in a mixture of water (200 ml.) and acetic acid (12.5 g.), and the mixture was heated at 40° for 10 min. After a few minutes at 40°, a colorless solid began to precipitate, and after 10 min. the contents of the flask had solidified. The product was filtered off, washed with water, and recrystallized (Norit) from boiling water (2 l.) to give 18.5 g. (86%) of β-3-methyl-2-quinoxalinylpropanoic acid as colorless, glistening needles, m.p. 164–168° (lit.[2] m.p. 167–168°).

Diethyl α-Benzoylglutarate (**9**). Ethyl benzoylacetate (96 g., 0.50 mole) was stirred and heated to 115°, sodium ethoxide (0.25 g.) was added, and to this stirred mixture ethyl acrylate (50 g., 0.50 mole) was added dropwise, the temperature being held at 120–130°. Addition was complete in 15 min.; the mixture was then held at 120° for a further 30 min. The cooled reaction mixture was taken up in ether, the ethereal solution was washed with water, dilute acetic acid, water, dilute sodium bicarbonate solution, and water, and finally dried ($MgSO_4$). Removal of the solvent left a viscous yellow oil which was distilled to give 139.5 g. (97%) of diethyl α-benzoylglutarate (**9**) as a colorless, viscous oil, b.p. 149–150° (0.06 mm.).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 66.13; H, 6.96.

γ-Benzoylbutanoic Acid (**10**). *Method A.* A solution of potassium hydroxide (10.0 g.) in water (200 ml.) was added to diethyl α-benzoylglutarate (10.0 g.) and the mixture was stirred overnight at room temperature. A solution of sodium nitrite (5 g.) in water (20 ml.) was added to the reaction mixture and the resulting solution was acidified at 10° with dilute sulfuric acid. After stirring at room temperature for 4 hr. the solution, which still gave a positive test for nitrous acid (starch–iodide paper), was extracted with ether. Removal of the ether left a colorless solid (5.50 g., 84%) m.p. 85–96°. Crystallization from a mixture of chloroform and petroleum ether (b.p. 60–70°) yielded colorless needles of γ-benzoylbutanoic acid (**10**), m.p. 127–128° (lit.[10] m.p. 128°).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.69; H, 6.32.

Method B. Diethyl α-benzoylglutarate (**9**, 33.0 g.) was added to 20% sodium hydroxide solution (200 ml.) and the mixture was refluxed for 2 hr., diluted to 1 l. with water, and acidified with 6 *N* hydrochloric acid. The precipitated γ-benzoylbutanoic acid (14.5 g.) was filtered off and the aqueous mother liquors were extracted with ether. Removal of the solvent gave a further 9.6 g. of product for a total yield of 24.1 g. (99%), m.p. 90–98°; the melting point was raised to 125–128° by recrystallization from chloroform–petroleum ether (b.p. 60–70°).

Methyl γ-Benzoylbutanoate (**11**). A mixture of glutaric anhydride (100 g.) and absolute methanol (75 ml.) was refluxed for 2 hr. Removal of excess methanol by evaporation under reduced pressure, followed by distillation *in vacuo*, gave 105.7 g. (84%) of γ-carbomethoxybutanoic acid as a colorless oil, b.p. 120–122° (1.5 mm.).

Thionyl chloride (45 g.) was added to γ-carbomethoxybutanoic acid (50 g.) and, when the evolution of hydrogen chloride had ceased, the mixture was refluxed for 1 hr. Excess thionyl chloride was removed under reduced pressure and the residue distilled to give 53.5 g. (95%) of γ-carbomethoxybutanoyl chloride as a colorless, mobile oil, b.p. 101–102° (16 mm.).[11]

γ-Carbomethoxybutanoyl chloride (53.0 g., 0.32 mole) was added dropwise over 2 hr. to a stirred suspension of anhydrous, sublimed aluminum chloride (93.5 g., 0.70 mole) in anhydrous benzene (200 ml.), the temperature being held at 40–50°. After addition was complete, the mixture was stirred and refluxed for a further 30 min. The cooled, deep brown reaction mixture was slowly poured onto a stirred mixture of concentrated hydrochloric acid (100 g.) and crushed ice (500 g.). The organic layer was separated, the aqueous layer was extracted with ether, and the combined extracts were washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Removal of the solvent and distillation gave 59.0 g. (89%) of methyl γ-benzoylbutanoate as a colorless, viscous oil, b.p. 127–128° (0.7 mm.).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.51; H, 7.09.

The semicarbazone derivative crystallized from aqueous methanol as colorless needles, m.p. 129–130°.

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.68; H, 6.11; N, 16.06.

γ-Oximino-γ-benzoylbutanoic Acid (**12**). Isoamyl nitrite (11.7 g., 0.1 mole) was added dropwise over 1 hr. to a stirred solution of methyl γ-benzoylbutanoate (20.6 g., 0.1 mole) in ether (250 ml.) containing concentrated hydrochloric acid (10 ml., 0.1 mole). The resulting mixture was stirred overnight at room temperature and then extracted with 10% sodium hydroxide solution (five 25-ml. portions). The combined alkaline extracts were poured onto a mixture of ice (500 g.) and concentrated hydrochloric acid (75 ml.), whereupon a colorless solid precipitated. This was filtered off, washed with ice-cold water, and recrystallized from 10% aqueous ethanol to give 20.1 g. (91%) of γ-oximino-γ-benzoylbutanoic acid as colorless needles, m.p. 150–152°.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.77; H, 5.02; N, 6.34.

β-3-Phenyl-2-quinoxalinylpropanoic Acid (**3a**). γ-Oximino-γ-benzoylbutanoic acid (1.35 g., 0.01 mole) was added to a solution of freshly crystallized *o*-phenylenediamine (1.08 g., 0.01 mole) in water (20 ml.) containing acetic acid (1.25 g.), and the mixture was refluxed for 5 min. The brown solid which precipitated on cooling was dissolved in dilute sodium hydroxide and treated with charcoal. Filtration and acidification gave 1.75 g. (62%) of β-3-phenyl-2-quinoxalinylpropanoic acid as a colorless solid, m.p. 158–160° (lit.[3] m.p. 162–163°).

(2-Carbomethoxyethyl)glyoxal-1-triphenylphosphazine (**13**). β-Carbomethoxypropionyl chloride[14] (6.0 g.) was added to an excess of a dry ethereal solution of diazomethane,[22] and the mixture was allowed to stand

(22) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

at room temperature for 3 hr. Distillation of the ether under reduced pressure left a pale yellow oil which showed a strong, sharp absorption at 2100 cm.$^{-1}$ in the infrared spectrum. This diazo ketone (6 g., 0.038 mole) was dissolved in anhydrous ether (30 ml., 20% solution), and to this solution was added a solution of triphenylphosphine (13.1 g., 0.05 mole) in anhydrous ether (35 ml., 30% solution). Almost immediately the glyoxal-1-triphenylphosphazine began to precipitate as pale yellow needles. The mixture was allowed to stand overnight at 0°, and the product was then filtered off, washed well with ether, and dried at 25° (0.01 mm.) for 30 min. to give 11.4 g. (71%) of product as a pale yellow crystalline solid, m.p. 138–142°, which slowly decomposed on standing. An analytical sample was prepared by crystallization from anhydrous ethanol as beautiful bright yellow needles, m.p. 142–144°.

Anal. Calcd. for $C_{24}H_{23}N_2O_3P$: C, 68.90; H, 5.50; N, 6.69; P, 7.41. Found: C, 69.23; H, 5.88; N, 6.65; P, 7.54.

(2-Carbomethoxyethyl)glyoxal (**14**). Hydrochloric acid (2 *N*, 21.6 ml.) was added dropwise over 1 hr. to a stirred, ice-cold suspension of (2-carbomethoxyethyl)-glyoxal-1-triphenylphosphazine (5.0 g., 0.012 mole) and sodium nitrite (1.824 g., 0.0264 mole) in anhydrous tetrahydrofuran (36 ml.). The mixture was stirred at room temperature for 1 additional hr., the organic layer was separated, the aqueous layer was extracted with ether, and the combined extracts were dried ($MgSO_4$). Removal of the solvent left a pale yellow unstable oil, contaminated with triphenylphosphine oxide. Attempted distillation of a sample, even under high vacuum, resulted in complete decomposition. When this oil was treated with an ethanolic solution of 2,4-dinitrophenylhydrazide the orange bis-2,4-dinitrophenylhydrazone separated immediately; it was purified for analysis by crystallization from dimethylformamide, from which it separated in long, feathery orange needles, m.p. 230–232°.

Anal. Calcd. for $C_{18}H_{16}N_8O_{10}$: C, 42.86; H, 3.20; N, 22.22. Found: C, 43.00; H, 3.18; N, 22.00.

1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoxalin-1-one (**4c**). A solution of β-quinoxalinylpropanoic acid (**3c**, 4.0 g.) in an excess of 1 *N* sodium hydroxide was shaken at room temperature with Raney nickel[23] (4 g.) catalyst[24] and hydrogen under 40 p.s.i. Uptake of hydrogen was complete in 3.5–4 hr., and the catalyst was filtered off. The pale yellow filtrate was acidified with 6 *N* sulfuric acid to give a colorless solution which turned yellow on standing at room temperature. After 2 hr., this solution was made alkaline again with 4 *N* sodium hydroxide, and a colorless solid precipitated immediately. Crystallization from ethanol gave 3.1 g. of the tricyclic amide (**4c**) as colorless needles, m.p. 162–165°. An analytical sample was prepared by further crystallization from ethanol and had m.p. 164–166°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.17; H, 6.47; N, 14.79.

The 5-N-acetyl derivative of **4c** was prepared as follows. A mixture of the tricyclic amide **4c** (0.5 g.), anhydrous pyridine (10 ml.), and acetic anhydride (2.5 ml.) was heated on a steam bath for 4 hr. The mixed solvents were distilled off under reduced pressure and the residual brown semisolid was sublimed at 140° (0.2 mm.) to give 0.52 g. of a pale yellow solid, m.p. 123–131°. An analytical sample was prepared by crystallization from 20% aqueous ethanol, from which it separated as colorless needles which melted diffusely over the range 131–139°. Repeated crystallization did not sharpen the melting point.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.10; H, 6.06; N, 12.31.

4-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoxalin-1-one (**4b**). Reductive cyclization of β-3-methyl-2-quinoxalinylpropanoic acid (**3b**) was carried out exactly as described for β-quinoxalinylpropanoic acid itself (**3c**). In the case of **3b**, however, acidification of the reaction mixture followed by basification resulted in precipitation of only ~60% of the product, which is appreciably soluble in water. Extraction of the aqueous mother liquors with chloroform after filtration gave the remainder of the cyclized material. The yields obtained were in the range 81–86%, and the product crystallized as colorless needles from benzene–petroleum ether (b.p. 60–70°), m.p. 151–154°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.50; H, 7.11; N, 13.54.

4-Phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoxalin-1-one (**4a**) was prepared similarly from β-3-phenyl-2-quinoxalinylpropanoic acid (**3a**), except that in this case complete reduction was observed only after hydrogenation had been allowed to proceed for 10 hr. The product, obtained in 60–70% yield, was a colorless solid which crystallized from 40% aqueous ethanol as beautiful, long colorless needles, m.p. 202–203°.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.43; H, 6.35; N, 10.34.

Quinoxaline-2-carboxaldehyde (**15**) was prepared in 61% yield by a previously described procedure.[16] The aldehyde was best purified by rapid sublimation at 120° (0.2 mm.) and was obtained as yellow needles, m.p. 105–107° (lit.[16] m.p. 108–109°).

Ethyl α-Carbethoxy-β-2-quinoxalinylpropenoate (**16**). A mixture of quinoxaline-2-carboxaldehyde (26.5 g., 0.17 mole), diethyl malonate (27.2 g., 0.17 mole), and piperidine (1 ml.) in absolute ethanol (200 ml.) was refluxed for 16 hr. and then allowed to stand at room temperature for a further 24 hr. The ethanol was distilled off under reduced pressure to leave a deep brown oil (54 g.) which was chromatographed on alumina (1 kg.). Elution with benzene gave 50.5 g. of a clear red oil which slowly solidified on standing. Crystallization from benzene gave 47.3 g. (87%) of ethyl α-carbethoxy-β-quinoxalinylpropenoate (**16**) as pale yellow needles, m.p. 76–79°. Further crystallization from benzene–petroleum ether (b.p. 60–70°) gave the product as pale yellow clusters of needles, m.p. 79–82°.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.79; H, 5.37; N, 9.29.

α-Carboxy-β-2-quinoxalinylpropenoic Acid (**17**). *Method A.* A solution of the diester **16** (1.20 g.) in ethanol (1 ml.) was added to a solution of barium hy-

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

(24) If equal weights of the propanoic acid and Raney nickel catalyst are not used, acidification of the hydrogenation mixture causes precipitation of unchanged propanoic acid. This can be filtered off and the cyclized material can be isolated by the above procedure.

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]

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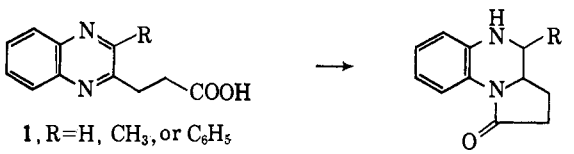
Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey. *Received October 9, 1964*

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.

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(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).