tical with that reported in earlier work.[4] The F^{19} n.m.r. spectrum showed three peaks at −54.0 (=NF), −2.8 (CF_3), and +8.2 p.p.m. (=CF), referred to CF_3COOH, with relative areas 1.0:2.2:1.2.

Acknowledgment.—We wish to thank Dr. Wallace S. Brey, University of Florida, for determining and interpreting the n.m.r. spectra given above. The analyses were performed by Galbraith Laboratories, Knoxville, Tenn. We are also indebted to Dr. Grover Paulett of the Redstone Arsenal Research Division, Rohm and Haas Co., Huntsville, Ala., for the mass spectroscopic analyses.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PRINCETON UNIVERSITY, PRINCETON, N. J.]

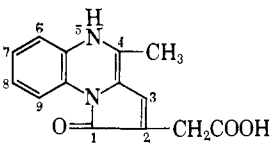
Synthesis and Properties of Pyrrolo(1,2-*a*)quinoxalines[1]

BY EDWARD C. TAYLOR AND GORDON W. H. CHEESEMAN

RECEIVED DECEMBER 6, 1963

The reaction of 2,3-dimethylquinoxaline with maleic anhydride in glacial acetic acid has recently been shown to give 2-carboxymethyl-4-methylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (1). In the present study, it has been found that fusion of maleic anhydride with 2-methyl-3-phenylquinoxaline gives 2-carboxymethyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (**13**). Decarboxylation of **13** gives 2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (**14**), the constitution of which is established independently by its synthesis in five steps from 2-methyl-3-phenylquinoxaline-1 N-oxide (**19**). Cyclodehydration of β-quinoxalylpropanoic acids with sulfuric acid–acetic anhydride, polyphosphoric acid, or phosphorus oxychloride is shown to be a useful and general synthetic route to the pyrrolo(1,2-*a*)quinoxaline system. Various chemical reactions of these compounds are described and their ultraviolet and n.m.r. spectra discussed.

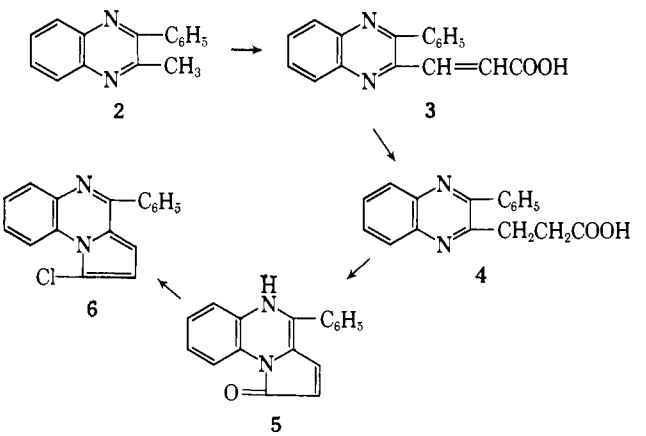
The reaction of 2,3-dimethylquinoxaline with maleic anhydride has recently been shown[2] to give 2-carboxymethyl-4-methylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (**1**) rather than the Diels–Alder adduct originally claimed. This novel entry into a 1,4-dihydroquinoxaline system, coupled with the interesting chemical



1

and physical properties of these tricyclic compounds, prompted us to look more closely into synthetic methods for their preparation and at their chemical properties. The present paper describes our more recent investigations in this field.

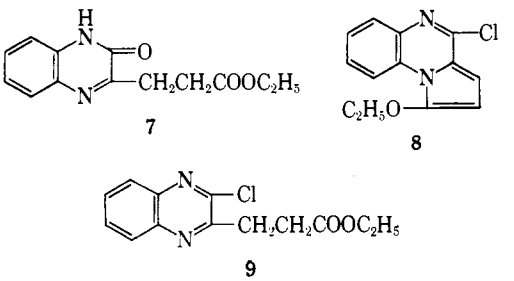
The synthesis of 4-methylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one from 2,3-dimethylquinoxaline and chloral, as described in our first communication, has now been extended to the synthesis of the corresponding 4-phenyl derivative **5**. Thus, the condensation of 2-methyl-3-phenylquinoxaline (**2**) with chloral followed by alkaline hydrolysis yielded the β-quinoxalylpropenoic acid **3** which was catalytically reduced to the saturated propanoic acid **4**. Cyclodehydration with a mixture of acetic anhydride and sulfuric acid then gave the tricyclic pyrroloquinoxaline **5**. Although its spectral characteristics were similar to those of the corresponding 4-methyl derivative, it proved to be difficult to characterize, and for this reason was converted with phosphorus oxychloride into 1-chloro-4-phenylpyrrolo(1,2-*a*)quinoxaline (**6**). This compound showed a long wave length absorption band at 346 mμ in contrast to the long wave length absorption band at 442 mμ for the 1,4-dihydroquinoxaline derivative **5**. The vinyl



2 **3** **4** **5** **6**

hydrogens in positions 2 and 3 of compound **6** appeared in the n.m.r. spectrum (CCl_4) as two doublets centered at 3.17 and 3.38 τ ($J \sim 5$ c.p.s.).

It has been reported recently[3] that the quinoxalylpropanoic acid ester **7** upon treatment with phosphorus oxychloride gave a mixture of **8** (in 18% yield) and **9** (in 45% yield). It thus appeared that this reagent might prove to be an effective cyclizing agent for quinoxalylpropanoic acids such as **4** or **10**. To test this possibility, the more readily available compound **10**[2] was treated directly with phosphorus oxychloride



7 **8** **9**

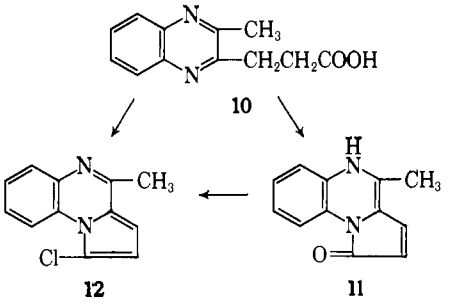
to give 1-chloro-4-methylpyrrolo(1,2-*a*)quinoxaline (**12**) in satisfactory yield. The n.m.r. spectrum (CCl_4)

(1) This investigation was supported by research grants to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CY-02551), and from the American Cancer Society.

(2) E. C. Taylor and E. S. Hand, *J. Am. Chem. Soc.*, **85**, 770 (1963).

(3) I. Kumashiro, *Nippon Kagaku Zasshi*, **82**, 1068 (1961).

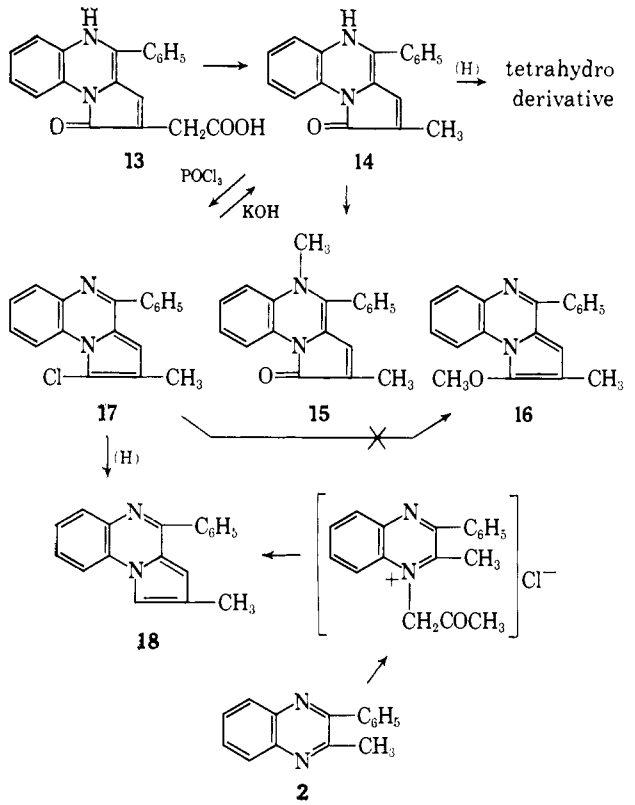
of this material showed the methyl group as an unsplit peak at 7.42 τ and the two vinyl hydrogens in positions 2 and 3 as two doublets centered at 3.30 and 3.43 τ ($J \sim 5$ c.p.s.). Compound **12** was also prepared by phosphorus oxychloride treatment of 4-methylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (**11**), which had previously been prepared[2] by acetic anhydride–sulfuric acid cyclodehydration of **10**. We now find that this latter conversion may also be effected by polyphosphoric acid. It would thus appear that several alternative methods are available for the conversion of β-quinoxalyl-substituted propanoic acids to the tricyclic pyrrolo(1,2-*a*)quinoxaline system.



Schönberg and Mustafa, in their original description of the dimethylquinoxaline–maleic anhydride reaction,[4] carried out the alleged Diels–Alder reaction by heating the two components in toluene solution. Bird and Cheeseman[5] recommended xylene in place of toluene. We had found during our reinvestigation of this reaction[2] that glacial acetic acid was a preferable solvent. We now wish to report that a marked improvement in yield and convenience can be achieved simply by fusing 2,3-dimethylquinoxaline with an excess of maleic anhydride. The unreacted maleic anhydride can be extracted from the fusion product with chloroform, thus yielding the substituted acetic acid derivative **1** in satisfactory yield. It was thought, however, that further investigations of the chemistry of this tricyclic system might better be carried out on the 4-phenyl adduct **13** rather than on **1** because the replacement of the methyl group in position 4 by a phenyl group not only removes an alternative site for cyclization, but also imparts to the compound more desirable physical characteristics. Our subsequent investigations on the chemistry of this 1,4-dihydroquinoxaline system were therefore carried out on compound **13**, the most readily accessible derivative in the series.

Compound **13** could be decarboxylated by vacuum sublimation to give 2-methyl-4-phenylpyrrolo(1,2-*a*)-quinoxalin-1(5H)-one (**14**) as large ruby-colored crystals. This compound proved to be stable to alkali. It was thought, for example, that alkaline cleavage of the amide linkage might lead to aromatization with loss of a hydride ion from position 5 to give a β-quinoxalylpropenoic acid, and that such a system might thereby function as an analog of DPNH. An even better reducing agent might be a reduced derivative of **14** in which removal of the potentially acidic proton in position 5 from conjugation with the carbonyl group might render the resulting compound more susceptible to alkaline hydrolysis. However, compound **14** could not be reduced under atmospheric pressure, regardless of the catalyst or medium employed. Other compounds in this series (*i.e.*, **13** and its methyl ester) were equally resistant to hydrogenation under similar conditions. Hydrogenation of **14** could be effected under high pressure (palladium-on-carbon catalyst in ethanol solution at 2000 p.s.i. of hydrogen) to give a colorless compound. This appeared to be a tetrahydro derivative which was further characterized by preparation of an acetyl derivative. However, the structure of this compound has not as yet been thoroughly established and is currently under investigation.

Treatment of compound **14** with methyl iodide in methanol containing sodium methoxide gave a monomethyl derivative which could have been either **15** or **16**. The long wave length absorption band displayed by this monomethyl product was strong evidence in favor of methylation on nitrogen at position 5 to give **15** rather than methylation on oxygen at position 1 to give **16** (see Table I). It would have been anticipated that compound **16** should have a maximum absorption

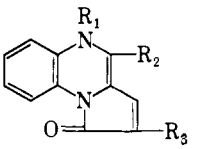


band rather characteristic of the 1-chloro derivatives **6** and **12**, which was not the case (see Table II). However, an attempt was made to confirm this structural assignment by an unequivocal synthesis of compound **16**. Thus, compound **14** was treated with phosphorus oxychloride to give 1-chloro-2-methyl-4-phenylpyrrolo-(1,2-*a*)quinoxaline (**17**) which, as anticipated, exhibited its maximum wave length absorption band at 342 mμ, is complete accord with observations on the previously prepared 1-chloro derivatives **6** and **12**. Its n.m.r. spectrum shows a single vinyl hydrogen peak at 3.18 τ and an unsplit methyl peak at 7.73 τ, with the aromatic hydrogens of the 4-phenyl group and the quinoxaline ring appearing further downfield. Most remarkably, compound **17** proved to be completely

(4) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 654 (1943).
(5) C. W. Bird and G. W. H. Cheeseman, *ibid.*, 3037 (1962).

TABLE I

ULTRAVIOLET SPECTRA OF PYRROLO(1,2-*a*)QUINOXALIN-1(5H)-ONES IN ABSOLUTE ETHANOL

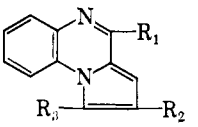


R_1	R_2	R_3							
H	C_6H_5	CH_2COOH	238 (26,700)	273 (19,300)	292[a] (15,100)		330[a] (4830)	340[a] (4070)
H	C_6H_5	CH_2COOCH_3	238 (26,700)	273 (19,900)	292[a] (15,400)		330[a] (4700)	340[a] (3840)
H	C_6H_5	CH_3	238 (27,900)	272 (19,200)	292[a] (14,600)		330[a] (4540)	340[a] (3870)
CH_3	C_6H_5	CH_3	238 (28,400)	264 (13,040)	297 (13,350)	303 (13,350)	330[a] (4110)	343[a] (3110)

[a] Denotes inflection point.

TABLE II

ULTRAVIOLET SPECTRA OF PYRROLO(1,2-*a*)QUINOXALINES IN ABSOLUTE ETHANOL



R_1	R_2	R_3										
H	H	OC_2H_5[a]	229.5 (30,900)	236[a] (27,500)	266[a] (9,550)	272 (11,000)	280 (9,550)	306[a] (2340)	318 (3800)	330 (5370)	367 (8510)	
Cl	H	OC_2H_5[a]	231 (37,150)	234[a] (37,150)		270 (14,100)	276[a] (12,300)	304[a] (3020)	314 (4680)	327 (6030)	362 (8910)	
Cl	H	OCH_3[a]	230 (33,900)	234[a] (33,100)		269 (12,900)	275[a] (11,500)		314 (4270)	326 (5750)	360 (8320)	
C_6H_5	H	Cl	233[a] (25,650)	240 (26,800)	243[a] (26,400)	272 (25,100)			323[a] (5040)	336 (8330)	346[a] (8100)	
CH_3	H	Cl	277 (28,000)	232[a] (25,950)	257[a] (14,300)					333 (9130)	347[a] (6270)	
CH_3	CH_3	Cl[b]	232 (28,800)	240[a] (26,800)	260[a] (12,600)					336 (9880)	349[a] (7120)	
C_6H_5	CH_3	Cl	235[a] (27,700)	244[a] (31,400)	248 (32,300)	276 (22,800)			328[a] (7940)		342 (9680)	
C_6H_5	CH_3	H	236[a] (25,500)	247[a] (31,650)	252 (33,200)	275 (20,600)					346 (9420)	

[a] Denotes inflection point. [b] Prepared from the 2,3-dimethylquinoxaline–maleic anhydride adduct (1) by decarboxylation followed by treatment with phosphorus oxychloride. Its ultraviolet and n.m.r. spectra (see Experimental) provide additional confirmation for the correctness of the structure assigned to 1.[2]

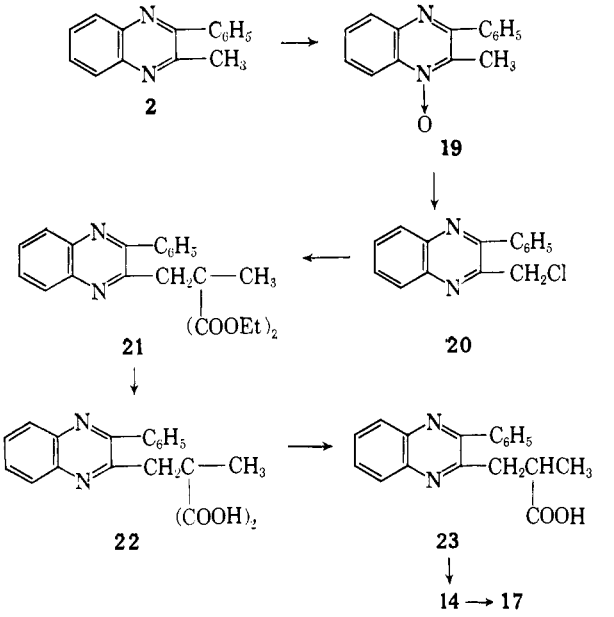
inert toward sodium methoxide. No replacement of chloride ion could be effected upon heating **17** with methanolic sodium methoxide for 28 hr. under reflux or by heating with methanolic hydrogen chloride for 6 hr. under reflux. It likewise proved to be unaffected by heating at 100° for 5 hr. with 2 *N* sulfuric acid. It was found, in fact, that hydrolysis of **17** could be carried out only by heating with potassium hydroxide in ethylene glycol. Since compound **17** is a vinylogous imino chloride, its stability both to acids and to alkaline cleavage is remarkable.

Catalytic reduction of **17** under atmospheric pressure yielded 2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxaline (**18**), which was characterized both as its hydrochloride and as its picrate. Care had to be taken to avoid absorption of more than 1 mole of hydrogen, for **18** is apparently rapidly converted to a more fully reduced material. The ease with which **18** reduces contrasts with the inertness of **14** under comparable conditions.

Finally, compound **18** was prepared independently and in a single step by the condensation of 2-methyl-3-phenylquinoxaline (**2**) with chloroacetone. The intermediate quaternary salt was not isolated, for it apparently cyclized spontaneously in the acid solution to give a mixture of **18** and the hydrochloride of **2**. A closely analogous reaction between chloroacetone and quinaldine has been reported[6] to give only the hydrochloride of quinaldine and not the expected quaternary salt.

The n.m.r. spectrum of **18** shows an unsplit methyl peak at 7.74 τ, in good agreement with the peak at 7.73 τ in the spectrum of **17**, also due to the 2-methyl group. A vinyl hydrogen peak at 3.29 τ is probably due to the 3-hydrogen, since the same hydrogen in **17** appears at 3.18 τ. A complex multiplet downfield which, by integration, represents a total of ten protons, is thus due to the vinyl hydrogen in position 1, as well as the remaining nine hydrogens of the 4-phenyl group and the quinoxaline ring.

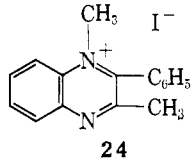
Although the structural assignments given to the maleic anhydride–methylquinoxaline products, and to the cyclodehydration products of β-quinoxalylpropanoic acids, appear to be firmly established both on chemical and on spectroscopic grounds, it was thought desirable to attempt an independent synthesis of compound **14**. This synthesis is outlined below.



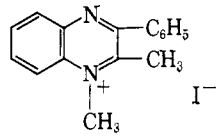
Treatment of 2-methyl-3-phenylquinoxaline (**2**) with 30% aqueous hydrogen peroxide in glacial acetic acid

(6) E. T. Burrows, D. O. Holland, and J. Kenyon, *J. Chem. Soc.*, 1069 (1946).

gave a mixture of the mono- and the di-N-oxide, from which the former was readily isolated as the major product by fractional crystallization. It is reasonable on electronic grounds to assign structure **19** to this product, but it should be noted that quaternization of 2-methyl-3-phenylquinoxaline with methyl iodide has been shown[7] to give the quaternary salt **24** rather than the expected product **25**. However, the structure of **19** was apparently confirmed by treatment with methanesulfonyl chloride[8] to give 2-chloromethyl-3-



24



25

phenylquinoxaline (**20**) in good yield. The presence of the $-CH_2Cl$ grouping in **20** was confirmed by the appearance of an unsplit methylene band at 5.19 τ (area ratio compared with aromatic protons of 2:9) in the n.m.r. spectrum (CCl_4). It was not possible to prepare the monohalogenated derivative by direct halogenation, for under the conditions investigated dihalogenation invariably takes place.[9] Compound **20** was treated with the sodium salt of diethyl methylmalonate to give the substituted malonic ester **21**. Subsequent hydrolysis to the dicarboxylic acid **22** followed by decarboxylation then gave α-methyl-β-(2-phenyl-3-quinoxalyl)propanoic acid (**23**), which was cyclized with acetic anhydride–sulfuric acid to give compound **14**, identical in every respect with the product of decarboxylation of the maleic anhydride adduct **13**. Furthermore, treatment with phosphorus oxychloride gave compound **17**, identical with the product obtained in the same manner from the decarboxylated adduct **14**. We thus consider the chemical structures of these pyrrolo(1,2-*a*)quinoxalines to be firmly established.

Experimental[10]

2-Carboxymethyl-4-methylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (**1**).—This material is better prepared by direct fusion of the reactants than by reaction in glacial acetic acid[2] or in xylene[5] as previously recommended. Thus, a finely ground mixture of 5.0 g. of 2,3-dimethylquinoxaline and 5.0 g. of maleic anhydride was heated briefly at 90°, and then allowed to react spontaneously until the vigorous exothermic reaction had subsided. The crude product was extracted with hot chloroform (to remove excess maleic anhydride) and washed with ethanol to give 6.5 g., 80%. The infrared spectrum of a sample crystallized from acetic acid and carefully dried at 100° *in vacuo* was identical with that of the adduct prepared as previously described.[2]

2-Methyl-3-phenylquinoxaline (**2**) was prepared by the following modification of the literature procedure.[11] To a solution of 14.8 g. (0.1 mole) of 1-phenylpropane-1,2-dione in 25 ml. of glacial acid, cooled by immersion in a water bath, was added 10.8 g. (0.1 mole) of *o*-phenylenediamine. After the initial exothermic reaction had subsided, the mixture was heated under reflux for 30 min. and then cooled. Addition of 20 ml. of water resulted in the separation of 14.5 g. of an oil which solidified upon refrigeration; m.p. 52–57°. Dilution of the filtrate with water gave an additional 6.15 g. of product, m.p. 56–57°, total yield 20.65 g. (96%). A sample sublimed at 50–55° (0.5 mm.) melted at 56–57° (lit.[11] m.p. 57–58°).

β-(3-Phenyl-2-quinoxalyl)propenoic Acid (**3**).—A solution of 13.0 g. of 2-methyl-3-phenylquinoxaline and 12 ml. of chloral in 10 ml. of pyridine was heated on a steam bath for 1 hr. The excess chloral and pyridine were then removed by evaporation under reduced pressure and the residue was dissolved in 30 ml. of ethanol. The solution was heated to boiling and 12 g. of sodium hydroxide dissolved in 20 ml. of water added cautiously. After the initial reaction had subsided, the mixture was heated under reflux for 10 min., cooled, and acidified with 2 *N* sulfuric acid. The precipitate which separated was collected by filtration, washed with water, dried, and extracted with 500 ml. of hot ethyl acetate. Cooling of the extract resulted in the crystallization of 3.45 g. (21%) of brownish yellow needles, m.p. 252–253° dec. Recrystallization from ethanol raised the melting point to 256–257° dec.

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.84; H, 4.54; N, 10.12.

β-(3-Phenyl-2-quinoxalyl)propanoic Acid (**4**).—A solution of 4.17 g. of β-(3-phenyl-2-quinoxalyl)propenoic acid in 25 ml. of 2 *N* sodium hydroxide and 150 ml. of water was stirred in an atmosphere of hydrogen with 0.5 g. of 5% palladium-on-carbon catalyst until 1 mole of hydrogen had been absorbed. The catalyst was filtered off and the filtrate was acidified with hydrochloric acid. The oil which separated was crystallized from benzene to give 2.97 g. (71%), m.p. 158–162°. Further recrystallization from aqueous methanol then gave yellow needles, m.p. 162–163°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.08; N, 10.07. Found: C, 73.49; H, 5.11; N, 10.29.

4-Phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (**5**).—A solution of 1.0 g. of β-(3-phenyl-2-quinoxalyl)propanoic acid in 50 ml. of acetic anhydride containing 10 drops of concentrated sulfuric acid was kept at 95° for 20 min. and then concentrated to a small volume under reduced pressure. The residual material was cooled to 0°, neutralized with 10% aqueous potassium hydroxide to pH 5, and the resulting precipitate crystallized from 50 ml. of glacial acetic acid to give 0.9 g. of dark-colored needles, m.p. >220° dec. The product was twice again recrystallized from glacial acetic acid; during each recrystallization some insoluble material formed which was discarded. An attempt was made to prepare a satisfactory analytical sample by sublimation at 220° (0.5 mm.) followed by recrystallization from ethanol, but the microanalytical results were consistently outside acceptable limits. The product was therefore characterized by conversion to 1-chloro-4-phenylpyrrolo(1,2-*a*)quinoxaline, as described below.

1-Chloro-4-phenylpyrrolo(1,2-*a*)quinoxaline (**6**).—The crude product (1.0 g.) obtained above by the acetic anhydride–sulfuric acid cyclodehydration of β-(3-phenyl-2-quinoxalyl)propanoic acid was heated under reflux for 1 hr. with 10 ml. of phosphorus oxychloride, the solution evaporated to dryness under reduced pressure; the residue was dissolved in chloroform and then poured over crushed ice. The organic layer was separated, washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The crude product (1.0 g., m.p. 140–145°) was extracted with two 40-ml. portions of petroleum ether (60–70°). The extracts upon cooling deposited 0.65 g. of colorless crystals, m.p. 143–145°.

Anal. Calcd. for $C_{17}H_{11}N_2Cl$: C, 73.25; H, 3.97; N, 10.05. Found: C, 73.38; H, 4.06; N, 10.05.

4-Methylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (**11**).—A mixture of 2.0 g. of β-(3-methyl-2-quinoxalyl)propanoic acid[2] and 20 g. of polyphosphoric acid was heated at 110° for 4 hr. After cooling, the mixture was quenched in ice–water and the pH adjusted to 7 with ammonium hydroxide. The precipitate was filtered off and extracted with excess sodium bicarbonate solution. The residual material (1.5 g.) was identified by comparison of its infrared spectrum and its chromatographic behavior (thin-layer, developed with ethyl acetate–methanol (90:10)) with an authentic sample,[2] and by its conversion with phosphorus oxychloride into 1-chloro-4-methylpyrrolo(1,2-*a*)quinoxaline, m.p. and mixture m.p. 97–98°.

1-Chloro-4-methylpyrrolo(1,2-*a*)quinoxaline (**12**).—A mixture of 2.0 g. of β-(3-methyl-2-quinoxalyl)propanoic acid[2] and 20 ml.

(7) A. H. Cook, J. Garner, and C. A. Perry, *J. Chem. Soc.*, 710 (1942).
(8) S. Cohen, E. Thom, and A. Bendich, *J. Org. Chem.*, **27**, 3545 (1962).
(9) G. M. Bennett and G. H. Willis, *J. Chem. Soc.*, 1960 (1928).
(10) Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Microanalyses were performed by the Spang Microanalytical Laboratories, Ann Arbor, Mich. Where appropriate, identity of compounds was confirmed by comparison of infrared spectra determined on a Perkin–Elmer Model 21 by the normal Nujol mull technique. All ultraviolet spectra were determined on a Cary Model 11 instrument, and the n.m.r. spectra on a Varian A-60.
(11) K. von Auwers, *Ber.*, **50**, 1177 (1917).

of phosphorus oxychloride was stirred and heated under reflux for 8 hr. Excess phosphorus oxychloride was removed by evaporation under reduced pressure and the residue was triturated with ice–water. A small amount (0.2 g.) of insoluble material was removed by filtration, and the filtrate was neutralized with sodium carbonate. Extraction of the aqueous solution with chloroform and evaporation of the dried chloroform extract gave 0.85 g. of crude product, m.p. 90–95°. Sublimation of this material then gave 0.77 g. (38%) of colorless needles, m.p. 93–94°. The analytical sample was prepared by further sublimation at 85° (0.25 mm.) and melted at 96–97.5°.

Anal. Calcd. for $C_{12}H_9N_2Cl$: C, 66.51; H, 4.18; N, 12.93. Found: C, 66.55; H, 4.30; N, 13.11.

1-Chloro-2,4-dimethylpyrrolo(1,2-*a*)quinoxaline.—A mixture of 2.0 g. of 2,4-dimethylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one[2] and 15 ml. of phosphorus oxychloride was heated under reflux for 1 hr. and then evaporated to dryness under reduced pressure. The residue was cautiously treated with ice–water and the precipitate which formed was collected by filtration and stirred with an excess of sodium bicarbonate solution. The insoluble material (2.0 g., 92%) melted at 106–108° and slowly sublimed when heated at 90–95° (0.5 mm.). Recrystallization of the crude product from petroleum ether (30–60°) gave colorless needles, m.p. 108–110°. The n.m.r. spectrum of this material (CCl_4) showed unsplit resonance lines at 7.81, 7.46, and 3.48 τ (area ratio 3:3:1) which are assigned to the 2-methyl group, the 4-methyl group, and the 3-vinyl hydrogen, respectively. The aromatic protons appear as a series of multiplets centered at 2.68, 2.19, and 1.15 τ.

Anal. Calcd. for $C_{13}H_{11}N_2Cl$: C, 67.68; H, 4.80; N, 12.15. Found: C, 67.73; H, 4.74; N, 12.20.

2-Carboxymethyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (13).—A mixture of 19.0 g. of 2-methyl-3-phenylquinoxaline and 57.0 g. of maleic anhydride was heated to 90° and then allowed to react spontaneously without further heating. Solid separated from the melt and the temperature rose to 120–130°. The heat of reaction was sufficient to maintain this temperature for approximately 15 min. The reaction mixture was then cooled, extracted with hot chloroform (to remove excess maleic anhydride), and the residue washed with ethanol to give 22.2 g. (81%). The analytical sample was prepared by rapid dissolution of the material in boiling glacial acetic acid followed by dilution with an equal volume of water. The material decomposed on heating above 240°.

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.42; N, 8.80. Found: C, 71.55; H, 4.32; N, 8.55.

Methyl Ester of 2-Carboxymethyl-4-phenylpyrrolo(1,2-*a*)-quinoxalin-1(5H)-one.—Dry hydrogen chloride was bubbled through a suspension of 3.4 g. of 2-carboxymethyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one in 100 ml. of dry methanol. The solid rapidly dissolved. After the solution had been saturated with hydrogen chloride, it was heated under reflux for 1 hr. and then concentrated to a small volume under reduced pressure. Addition of an excess of aqueous sodium acetate to the residue resulted in the separation of a solid which was recrystallized from a mixture of 150 ml. of methanol and 100 ml. of water to give 2.7 g. of the desired ester. An additional 0.5 g. of product was obtained by concentration of the mother liquor; total yield 3.2 g. (90%), m.p. >220° dec.

Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.86; N, 8.43. Found: C, 72.33; H, 4.77; N, 8.40.

2-Methyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (14).—2-Carboxymethyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one was decarboxylated by heating 4.0-g. portions for approximately 12 hr. at 260–270° under a pressure of 0.5 mm. The combined sublimates from 16.0 g. of the maleic anhydride adduct totaled 9.0 g. Recrystallization from aqueous ethanol gave 8.1 g. (59%) of product, m.p. >250° dec.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.82; H, 5.15; N, 10.21. Found: C, 78.68; H, 4.93; N, 10.31.

Tetrahydro Derivative of 2-Methyl-4-phenylpyrrolo(1,2-*a*)-quinoxalin-1(5H)-one.—A solution of 3.0 g. of 2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one in 100 ml. of ethanol was hydrogenated in the presence of palladium-on-carbon catalyst at 2000 p.s.i. and at 70° for 6 hr. The catalyst was removed by filtration and the ethanol evaporated under reduced pressure. Recrystallization of the residue (Norit) from ethanol gave 0.95 g. of crude tetrahydro derivative. This material was dissolved in benzene and chromatographed on a column of alumina. Elution with benzene–ether gave a fraction which after recrystallization from ethanol melted principally from 170–176°; $\lambda_{max}^{C_2H_5OH}$ 231, 262 (infl.), 319 mμ (ε 22,400, 8360, 5700).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.35, 77.53; H, 6.28, 6.33; N, 10.00, 10.11.

Conversion of this material to an acetyl derivative was accomplished as follows: A mixture of 0.45 g. of the tetrahydro compound and 10 ml. of acetic anhydride was heated under reflux for 2 hr. and then evaporated to a small volume under reduced pressure. Water was added to the residue and the precipitated solid (0.50 g., m.p. 128–132°) crystallized from aqueous methanol to give 0.36 g., m.p. 136–138°; $\lambda_{max}^{C_2H_5OH}$ 235, 267 mμ (ε 20,450, 16,200).

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.75. Found: C, 75.07; H, 6.31; N, 8.66.

2,5-Dimethyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (15).—A solution of 1.37 g. of 2-methyl-4-phenylpyrrolo(1,2-*a*)-quinoxalin-1(5H)-one in methanolic sodium methoxide (prepared from 0.23 g. of sodium and 100 ml. of methanol) containing 5 ml. of methyl iodide was heated under reflux in a nitrogen atmosphere until it was no longer alkaline, and at this point an additional portion of methyl iodide and methanolic sodium methoxide was added. When the reaction mixture had become neutral after further refluxing, it was concentrated to a small volume under reduced pressure. Addition of water to the residue followed by filtration gave a crude product which was crystallized from ethyl acetate and then from aqueous methanolic sodium hydroxide to give 0.22 g. (15%), m.p. 234–237°. The analytical sample, prepared by sublimation at 200° (0.5 mm.) followed by recrystallization from ethyl acetate, melted at 235–237°.

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.15; H, 5.59; N, 9.72. Found: C, 79.10; H, 5.69; N, 9.61.

1-Chloro-2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxaline (17).—A mixture of 5.0 g. of 2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one and 40 ml. of phosphorus oxychloride was heated under reflux for 1 hr., the excess phosphorus oxychloride was removed by evaporation under reduced pressure, and the residue was cautiously treated with ice–water. The precipitate which formed was collected by filtration and triturated with an excess of sodium bicarbonate solution to give 4.75 g. (89%), m.p. 150–153°. The analytical sample, prepared by recrystallization from acetone followed by methanol, melted at 157–158°.

Anal. Calcd. for $C_{18}H_{13}N_2Cl$: C, 73.83; H, 4.47; N, 9.57. Found: C, 73.68; H, 4.53; N, 9.55.

Hydrolysis of this chloro compound back to **14** could be effected as follows: A mixture of 0.50 g. of the above chloro compound in a solution of 1.0 g. of potassium hydroxide in 10 ml. of ethylene glycol was heated under reflux for 45 min., cooled, and then poured into water. The pH was adjusted to 5 with acetic acid, and the resulting precipitate was collected by filtration and crystallized from aqueous acetic acid to give 0.22 g. of 2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one, identical with an authentic sample. No displacement of chloride ion could be effected by heating the chloro compound with methanolic sodium methoxide for 28 hr. under reflux, by heating with methanolic hydrogen chloride for 6 hr. under reflux, or by heating with 2 *N* sulfuric acid for 5 hr. at 100°.

2-Methyl-4-phenylpyrrolo(1,2-*a*)quinoxaline (18).—Platinum catalyst, prepared by prereducing 0.2 g. of platinum oxide in methanol, was added to a solution of 1.46 g. of 1-chloro-2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxaline in 50 ml. of methanolic hydrogen chloride. The mixture was stirred in an atmosphere of hydrogen until 1 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. A mixture of aqueous sodium carbonate and chloroform was added to the residue, the organic layer was separated, washed with water, dried, and evaporated. A portion of the residual oil was converted into a picrate, m.p. 248° dec., by treatment with methanolic picric acid solution.

Anal. Calcd. for $C_{18}H_{14}N_2 \cdot C_6H_3N_3O_7$: C, 59.14; H, 3.52. Found: C, 59.14; H, 3.37.

The remainder of the residual oil was converted into a hydrochloride salt by treatment with 2 *N* hydrochloric acid, followed by crystallization from methanolic hydrogen chloride and ether (1:1).

Anal. Calcd. for $C_{18}H_{14}N_2 \cdot HCl$: C, 73.33; H, 5.13; N, 9.51. Found: C, 73.01; H, 5.27; N, 9.58.

2-Methyl-4-phenylpyrrolo(1,2-*a*)quinoxaline (**18**) was prepared independently by the condensation of chloroacetone (8.4 g.) with 2-methyl-3-phenylquinoxaline (6.6 g.) in 10 ml. of eth-

anol at 125–135° for 3 days, followed by evaporation to dryness and extraction with ether. Examination of the infrared spectrum of the residue (4.0 g.) showed it to be a mixture of **18** and the hydrochloride of 2-methyl-3-phenylquinoxaline. The latter was removed by further extraction with hot 2 *N* hydrochloric acid to give a solid residue which proved to be identical with compound **18** prepared as described above, as judged by a comparison of both infrared and ultraviolet spectra.

2-Methyl-3-phenylquinoxaline-1 N-Oxide (19).—A solution of 4.4 g. of 2-methyl-3-phenylquinoxaline in a mixture of 40 ml. of glacial acetic acid and 15 ml. of aqueous hydrogen peroxide (30%) was heated at 56° for 14 hr. The mixture was then concentrated to a small volume under reduced pressure; the residue was adjusted to pH 7 with 10% aqueous potassium hydroxide and extracted with chloroform. Evaporation of the chloroform extract gave an oil which upon extraction with 150 ml. of hot petroleum ether (60–70°) followed by cooling gave 2.2 g. (47%) of product, m.p. 96–100°. Two recrystallizations from methanol raised the melting point to 104–106°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.24; H, 5.12; N, 11.86. Found: C, 76.01; H, 5.33; N, 11.81.

The undissolved residue from the petroleum ether extraction was crystallized from ethanol and then from benzene to give yellow crystals of 2-methyl-3-phenylquinoxaline-1,4 di-N-oxide, m.p. 193–195°. This material is reported[12] to melt at 193–194°.

2-Chloromethyl-3-phenylquinoxaline (20).—A mixture of 5.0 g. of 2-methyl-3-phenylquinoxaline-1 N-oxide and 10 ml. of methanesulfonyl chloride was set aside at room temperature. Within 1 hr., the solid had dissolved, and after 24 hr. the solution was poured into a mixture of methylene chloride and water. The organic layer was separated, washed with an excess of aqueous sodium acetate solution, and dried over anhydrous sodium sulfate. Evaporation first under water pump pressure and then at 75° (1.5 mm.) (to remove any excess methanesulfonyl chloride) gave an oily residue which was dissolved in benzene and passed through a column of alumina. Elution with benzene gave 2.75 g. (51%) of 2-chloromethyl-3-phenylquinoxaline, m.p. 110–114°; continued elution with benzene and then with benzene–ether furnished an orange oil (not characterized) and then unchanged 1-N-oxide (0.8 g.). Recrystallization of the product from petroleum ether (60–70°) gave 2.3 g., m.p. 118–120°.

Anal. Calcd. for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.84; H, 4.25; N, 11.08.

Ethyl α-Carbethoxy-α-methyl-β-(3-phenyl-2-quinoxalyl)propanoate (21).—A mixture of 4.5 g. of 2-chloromethyl-3-phenylquinoxaline, 50 ml. of toluene, and diethyl sodiomethylmalonate (prepared from 3.48 g. of diethyl methylmalonate and 0.46 g. of sodium) was stirred and heated under reflux for 9 hr. and then cooled. Water was added and the organic layer was separated, washed with water, and dried over anhydrous sodium sulfate. After evaporation of solvent and excess diethyl methylmalonate *in vacuo*, the residue was dissolved in benzene and passed through a column of alumina. The initial eluent contained unchanged 2-chloromethyl-3-phenylquinoxaline, m.p. 114–117°; the middle fractions (1.5 g., m.p. 82–117°) contained a mixture of starting material and product; continued elution with benzene then gave 2.5 g. (39%) of the desired product, m.p. 98–99°. The analytical sample, m.p. 100–101°, was prepared by recrystallization from petroleum ether (30–60°), followed by recrystallization from aqueous methanol.

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.40; H, 6.19; N, 7.14. Found: C, 70.48; H, 6.11; N, 7.17.

α-Carboxy-α-methyl-β-(3-phenyl-2-quinoxalyl)propanoic Acid (22).—A mixture of 1.96 g. of the diethyl ester was heated under reflux with 10 ml. of 2 *N* sodium hydroxide and 10 ml. of ethanol for 3 hr.; the ethanol was then removed by evaporation under reduced pressure. The residual solution was treated with Norite and the filtrate acidified with hydrochloric acid. The precipitate which formed was collected by filtration, dried, and extracted with benzene to give the desired product; yield 1.33 g., m.p. *ca.* 130° dec. The analytical sample, m.p. *ca.* 120–122° dec., was prepared by recrystallization from aqueous ethanol. It retained some solvent of crystallization even after prolonged drying *in vacuo* at 56°.

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.84; H, 4.80; N, 8.33. Calcd. for $C_{19}H_{16}N_2O_4 \cdot C_2H_5OH$: C, 65.95; H, 5.81; N, 7.33. Found: C, 66.64, 66.45; H, 6.06, 5.93; N, 6.95, 6.75.

α-Methyl-β-(3-phenyl-2-quinoxalyl)propanoic Acid (23).—The dicarboxylic acid described above (1.33 g.) was heated at 135° for 1 hr. and the residue cooled and partitioned between chloroform and saturated sodium bicarbonate solution. Acidification of the aqueous phase gave 0.90 g. (78%) of the desired propanoic acid, m.p. 164–166°. The melting point was raised to 166–167° by recrystallization from aqueous methanol.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.86; H, 5.51; N, 9.46.

2-Methyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one (14) by Cyclization of 23.—To a mixture of 30 ml. of acetic anhydride and 6 drops of concentrated sulfuric acid, preheated to 95° on a steam bath, was added 0.60 g. of α-methyl-β-(3-phenyl-2-quinoxalyl)propanoic acid (**23**). The resulting solution was maintained at 95° for 20 min. and then concentrated to a small volume under reduced pressure. Water was added to the residue and the pH adjusted to 5 with sodium carbonate. The precipitate which separated was collected by filtration and crystallized from aqueous ethanol (1:2) to give 0.19 g. of 2-methyl-4-phenylpyrrolo(1,2-*a*)quinoxalin-1(5H)-one, identical in every respect with an authentic sample prepared as described above by decarboxylation of the adduct formed from 2-methyl-3-phenylquinoxaline and maleic anhydride. The cyclodehydration product was further characterized by conversion with phosphorus oxychloride into 1-chloro-2-methyl-4-phenylpyrrolo-(1,2-*a*)quinoxaline, m.p. and mixture m.p. 158–159°.

Dilution of the aqueous ethanolic mother liquor gave 0.2 g. of solid which, by examination of its infrared spectrum, proved to contain unchanged starting material. This was treated with acetic anhydride–sulfuric acid as described above to give an additional 0.11 g. of product; total yield 0.30 g. (53%).

(12) J. K. Landquist and G. J. Stacey, *J. Chem. Soc.*, 2822 (1953).

[CONTRIBUTION FROM THE EVANS CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY, COLUMBUS 10, OHIO]

The Synthesis and Ionization Constants of the Six Aminobenzo[c]phenanthrenes[1]

BY MELVIN S. NEWMAN AND JOCHANAN BLUM[2]

RECEIVED NOVEMBER 15, 1963

2-, 3-, 4-, 5-, and 6-aminobenzo[c]phenanthrene were made by Curtius rearrangement of the corresponding acid azides, followed by alkaline hydrolysis of the resulting isocyanates. 1- and 2-aminobenzo[c]phenanthrene were made by Bucherer reactions from the corresponding hydroxy compounds. The ionization constants of these amines were determined. The ultraviolet absorption spectra of the amines and their hydrochlorides were determined. 3-Methyl- and 4-methylbenzo[c]phenanthrene were made by new routes.

The interest in preparing the six isomeric monosubstituted derivatives of benzo[c]phenanthrene (I) has been discussed previously.[3] The ionization constants of the six carboxybenzo[c]phenanthrenes[4] and of the six hydroxybenzo[c]phenanthrenes[3] have been

(1) This research was supported by a grant from the National Institutes of Health, Bethesda, Md.

(2) Postdoctoral Fellow, 1963.

(3) See discussion: (a) in M. S. Newman and J. Blum, *J. Am. Chem. Soc.*, **86**, 503 (1964); (b) M. S. Newman and D. K. Phillips, *ibid.*, **81**, 3667 (1959).

(4) M. S. Newman and H. Boden, *ibid.*, **83**, 115 (1961).