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STRUCTURE OF THE ALLEGED DIELS-ALDER ADDUCT FROM 2,3-DIMETHYLQUINOXALINE AND MALEIC ANHYDRIDE[1]

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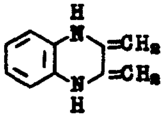
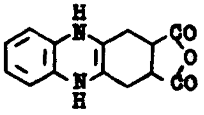
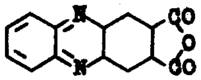
Frequent reference is made in the literature[2] to the Diels-Alder reaction of 2,3-dimethylquinoxaline (purportedly reacting in its tautomeric form I) with maleic anhydride to give the "adduct" IIa or IIb. This compound is reported[2a] to have the elementary analysis $C_{14}H_{12}N_2O_3$, not to melt below 300°, to be yellow, sublimable, unreactive towards diazomethane, and to be recrystallizable from acetic acid, soluble in aqueous 10°/o sodium hydroxide, and recoverable after refluxing for one hour in aqueous 10°/o sodium hydroxide. Since the stability of the compound seemed at variance with its assigned


I


IIa


IIb

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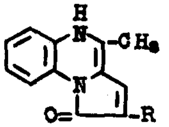
[1] This work was supported by a grant (CY-2551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

[2] (a) A. Schönberg and A. Mustafa, J. Chem. Soc. 654 (1943), cited in
(b) L.H. Flett and W.H. Gardner, Maleic Anhydride Derivatives, John Wiley and Sons, Inc., New York, 1952, p. 153;
(c) E.H. Rodd, ed., Chemistry of Carbon Compounds, Vol. IVB, Elsevier Publishing Company, Amsterdam, 1959, p. 1349;
(d) A. Albert, Heterocyclic Chemistry, The Athlone Press, University of London, 1959, p. 89;
(e) M.C. Kloetzel, Organic Reactions, Vol. IV, John Wiley and Sons, Inc., New York, 1948, p. 39;
(f) J.C.E. Simpson, The Chemistry of Heterocyclic Compounds: Condensed Pyridazine and Pyrazine Rings, Interscience Publishers, Inc., New York, 1953, p. 278.

dihydroquinoxaline structure, its recovery from boiling dilute sodium hydroxide solution inexplicable in terms of the anhydride grouping, and its yellow color questionable in terms of either IIa or IIb, we have reinvestigated the reaction and wish to propose structure III for the alleged Diels-Alder "adduct".[3]



III: R = $-CH_2COOH$
IV: R = $-CH_3$
VIII: R = $-H$

Repetition of the reaction of 2,3-dimethylquinoxaline with maleic anhydride under the previously described conditions[2a] gave a product which, after repeated crystallizations from acetic acid, had the correct analysis, did not melt below 300° and could indeed be recovered from basic solution by acidification. Its infrared spectrum, however, lacked the typical anhydride absorption bands, but showed the presence of an -OH or -NH group (3.07 μ), a carboxylic acid group (broad bands at 4.2 and 5.3, band at 5.87 μ), a double bond (5.99 μ) and probably a vinylogous amide (6.19, 6.26, 6.40, 6.54 μ).[4] A Kuhn-Roth determination showed the presence of at least one C-CH_3 group[5] (found 4.3 °/o; required 5.9 °/o). The presence of one carboxyl group was demonstrated by the formation of a monomethyl ester, $C_{15}H_{14}N_2O_3$ by treatment of the "adduct" with excess diazomethane. On sublimation the "adduct" lost the elements of CO_2 to give IV, $C_{13}H_{12}N_2O$, which contains at least two C-CH_3 groups by Kuhn-Roth determination (found 9.4 °/o; required 14.2 °/o). Thus the group $-CH_2COOH$ is present

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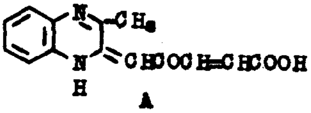
[3] A revised but incorrect formulation (A) for this "adduct" has very recently been advanced (C.W. Bird and G.W.H. Cheeseman, J. Chem. Soc. 3037 (1962).

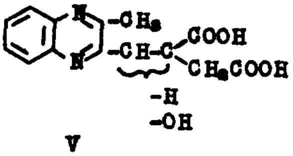


A

[4] N.H. Cromwell, F.A. Miller, A.R. Johnson, R.L. Frank, and D.J. Wallace, J. Am. Chem. Soc. 71, 3337 (1949).

[5] B. Franck and J. Knoke, Ber. 95, 579 (1962).

in the "adduct". Further evidence that the carboxylic acid group is insulated from the chromophoric system is the fact that the ultraviolet spectra of III, its methyl ester, and the decarboxylation product IV are nearly identical. The n.m.r. spectrum of the "adduct" (III) in KOH/D_2O showed unsplit bands at 8.06, 6.67, 3.39, 3.22 and 1.2 τ (approximate area ratio 3:2:1:4:1 respectively), consistent with the presence of a methyl group, a methylene group, a vinyl hydrogen, aromatic hydrogens and an N-H group.



V

Oxidation of the "adduct" with alkaline potassium ferricyanide gave an unstable product (approximate analysis, $C_{14}H_{14}N_2O_5$, m.p. 142° dec.) to which structure V (the tertiary position for the hydroxyl group is favored for theoretical reasons) is assigned on the basis of the following evidence: (i) its ultraviolet spectrum (λ_{max}^{EtOH} 240, 310 (infl.), 320, 328 (infl.) mμ; λ_{min} 283 mμ) is similar to that of 2,3-dimethylquinoxaline (λ_{max}^{EtOH} 236, 240 (sh), 317, 322 (infl.) mμ; λ_{min} 260 mμ); (ii) its infrared spectrum indicates the presence of -OH (2.87 μ) and -COOH (3.7-4.5, 5.0-5.5, 5.85 (broad) and 6.0 (sh) μ) groups; (iii) its neutral equivalent weight was found to be 154 (calc. 145); (iv) treatment with diazomethane followed by chromatography gave a dimethyl ester, $C_{16}H_{16}N_2O_4$, whose infrared spectrum indicates the presence of both a saturated (5.75 μ) and an α,β-unsaturated (5.82 μ) ester, and whose n.m.r. spectrum ((CCl_4): multiplet center 2.33, 6.06, 6.20, 6.43 and 7.24 τ; approximate area ratio 5:2:3:3:3) is readily interpretable in terms of structure VI[6]; (v) on heating at its melting point, it was converted

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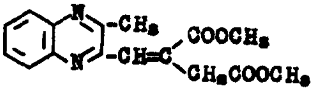
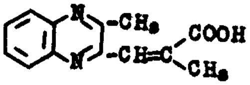
[6] The configuration about the double bond is not known.

to a monocarboxylic acid VII[6], $C_{13}H_{12}N_2O_2$, m.p. 185-186° (λ^{EtOH}_{max} 243 (infl.), 259, 330 mμ ; λ_{min} 286 mμ ; *cf.* compound X, λ^{EtOH}_{max} 242 (infl.), 260, 335, 342 mμ ; λ_{min} 286 mμ), which upon hydrogenation gave a saturated acid, $C_{13}H_{14}N_2O_2$, m.p. 136-137°, exhibiting a typical 2,3-dialkylquinoxaline ultraviolet spectrum.



VI



VII

Finally, a model compound, $C_{12}H_{10}N_2O$, containing the vinylogous amide system present in III, was synthesized as outlined below. 2,3-Dimethylquinoxaline was condensed with chloral[7] to give IX, $C_{12}H_{11}N_2OCl_3$, m.p. 147-148°, which upon treatment with strong base[8] gave the unsaturated acid, X, $C_{12}H_{10}N_2O_2$, m.p. 215° dec. The latter compound was alternatively obtained, but in poor yield, by sodium borohydride reduction of ethyl 2-methylquinoxal-3-ylpyruvate (XI)[9] to give the hydroxy ester XII, $C_{14}H_{16}N_2O_3$, m.p. 77-78°, followed by dehydration with concentrated sulfuric acid. Hydrogenation of X gave the saturated acid (methyl ester, $C_{13}H_{14}N_2O_2$, m.p. 97-98°) which was cyclized to VIII with acetic anhydride in the presence of sulfuric acid.

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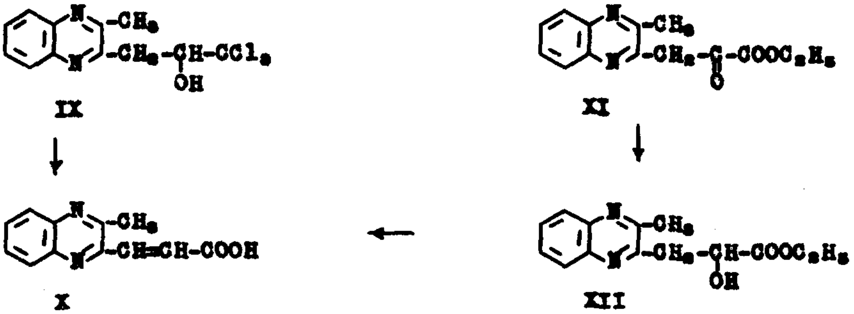
[7] For analogous condensations with chloral see R.G. Jones, E.C. Kornfeld and K.C. McLaughlin, *J. Am. Chem. Soc.* **72**, 3539 (1950).

[8] Hydrolysis of chloral adducts to α,β-unsaturated acids has been reported by R.B. Woodward and E.C. Kornfeld, *J. Am. Chem. Soc.* **70**, 2508 (1948) and by Jones *et. al.* (Ref.7).

[9] W. Borsche and W. Doeller *Ann.* **537**, 39 (1939).



The infrared spectra of the decarboxylation product IV and compound VIII are almost identical in the region 2-7 μ , except for slight differences in band intensities. Furthermore, the complex ultraviolet spectra of the "adduct" III, its methyl ester, and the decarboxylation product IV are almost identical with the spectrum of the model compound VIII (see Table I). The long wavelength

Table I

Ultraviolet Spectral Data ($\lambda_{max}^{C_2H_5OH}$)

III		IV		VIII	
mμ	ϵ	mμ	ϵ	mμ	ϵ
233	24,900	234	21,800	231	24,900
258	7,000	259	5,700	257	8,100
291	9,400	291	8,300	288	9,600
299	9,900	299	8,500	297	10,400
325	2,900	325	2,500	323	2,700
420	12,900	415	11,300	421	11,700

maximum of these compounds appears to be characteristic of 1,4-dihydroquinoxalines and 1,4-dihydropyrazines which possess a carbonyl group in conjugation

with the double bond[10].

It may be noted that 2-methylquinoxaline and maleic anhydride form a condensation product, $C_{13}H_{10}N_2O_3$, which is analogous to compound III.

It is also interesting to note that the reaction of 2-methylquinoxalines with maleic anhydride, and the dehydrative cyclization of β-quinoxal-2-ylpropionic acids, represent novel synthetic routes to 1,4-dihydroquinoxalines (e.g., III, VIII). If these procedures prove to be general for other condensed pyrazine heterocycles, we would have in hand, as an example, a simple synthesis of 5,8-dihydropteridines, a difficultly accessible structural type which is assuming considerable importance in biological systems. Extensions of these reactions to other heterocyclic systems are under investigation.

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[10] (a) J.A. Barltrop, C.G. Richards and D.M. Russell, J. Chem. Soc. 1423 (1959);
(b) F.E. King and J.W. Clark-Lewis, J. Chem. Soc. 3080 (1951);
(c) W. Pfleiderer and E.C. Taylor, J. Am. Chem. Soc. 82, 3765 (1960);
(d) H.I.X. Mager and W. Berends, Rec. trav. Chim. 79, 282 (1960) and preceding papers in this series.