Anal. Calcd. for $C_{13}H_7BrF_3NO_4S_2$: C, 35.30; H, 1.60. Found: C, 35.16; H, 1.67.

A similar synthesis of XV using XIII instead of XII gave only a 46% yield after refluxing for as long as 18 hr.

2'-Bromo-2-amino-4-trifluoromethylsulfonyldiphenylsulfide (XVII). A vigorous stream of hydrogen chloride gas was passed into a suspension of 450 g. (2.0 mol.) of stannous chloride dihydrate in 450 ml. of glacial acetic acid and 35 ml. of water until the suspension cleared (*ca.* 10 min.). The temperature of this solution was raised to 65° and 74 g. (0.17 mol.) of XV was added in portions during 1 hr., keeping the temperature at 70–80°. After about two-thirds of the stannous chloride had been added a white solid began to form. On completion of the addition, the reaction mixture was stirred at 85–90° for 2 additional hr. The mixture was filtered and the filtrate was poured onto crushed ice. The resulting precipitate was recrystallized from 95% ethanol to give 58 g. (84%) of white crystals; m.p. 112–113°.

Anal. Calcd. for $C_{13}H_9BrF_3NO_2S_2$: C, 37.87; H, 2.20. Found: C, 38.06; H, 2.40.

2'-Bromo-2-formamido-4-trifluoromethylsulfonyldiphenylsulfide (XVIII). A mixture of 100 g. (0.22 mol.) of XVII and 1 l. of 90% formic acid was refluxed for 20 hr. and poured over 6 l. of crushed ice. The resulting precipitate was washed with water and crystallized from ethanol to give 77 g. (72%) of white needles; m.p. 102.5–103°.

Anal. Calcd. for $C_{14}H_9BrF_3NO_3S_2$: C, 38.19; H, 2.06. Found: C, 38.44; H, 2.17.

2-Trifluoromethylsulfonylphenothiazine (XX) (from XVII). A mixture of 28 g. (0.07 mol.) of XVII, 250 ml. of DMF, 11.6 g. (0.08 mol.) of anhydrous potassium carbonate and 1.4 g. of copper-bronze powder was stirred and refluxed under dry nitrogen, for 6.5 hr. The reaction was then stopped even though carbon dioxide was still being evolved. The reaction mixture was filtered hot, the solid material washed with 25 ml. of DMF and the combined filtrate and washings were poured into 3 l. of water. A yellow colloid formed initially but on standing overnight an orange precipitate separated. The precipitate was dissolved in ethanol, treated with a mixture of chromatographic alumina and Darco G-60, and the solution was diluted with water to give 14 g. (60%) of orange crystals; m.p. 146–147°.

Anal. Calcd. for $C_{13}H_8F_3NO_2S_2$: C, 47.12; H, 2.43. Found: C, 47.27; H, 2.56.

A similar small scale (0.003 mol.) cyclization which was allowed to stir and reflux for 24 hr. gave only 30% of XX.

(*From* XVIII). A mixture of 11 g. (0.025 mol.) of XVIII, 125 ml. of DMF, 4.2 g. (0.03 mol.) of anhydrous potassium carbonate and 0.5 g. of copper-bronze powder was refluxed and stirred, under dry nitrogen, until carbon dioxide evolution was complete (1.25 hr.). The reaction mixture was filtered and washed as in Method A and the combined filtrate and washings were poured into a l. of cold water. On standing at room temperature for 2 hr. the initially formed yellow colloid gave 6.6 g. (80%) of orange crystals, m.p. 145–146° (XX). A mixed melting point with the material obtained from XVII showed no depression.

Acknowledgment. The authors wish to express their appreciation to Dr. James W. Wilson for his advice and suggestions concerning this work. The assistance of the Research Analytical Section of Smith Kline & French Laboratories for obtaining spectral and analytical data is gratefully acknowledged.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH AND THE DEPARTMENT OF CHEMISTRY, TEMPLE UNIVERSITY]

Azacyclooctane Derivatives[1]

JULIUS DIAMOND,[2a] WILLIAM F. BRUCE,[2b] CARL GOCHMAN,[2b] AND FLOYD T. TYSON[2c]

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Preparation of 1-methyl-4-phenyl-4-carbethoxyazacyclooctane and α-1,3-dimethyl-4-phenyl-4-propionoxyazacyclooctane is described. These substances showed less analgesic activity than their analogs with six-membered rings.

The preparation of ethoheptazine[3] has made available a seven-membered ring analog of meperidine. This new compound has proved to have valuable analgesic properties without addiction potential.[4] Continuing this study, we have now made the eight-membered ring analog of meperidine to permit study of the effect of further ring enlargement, and particularly because the morphine molecule can be considered to contain an eight-membered heterocyclic ring. In addition to the eight-membered ring analog in this series, namely 1-methyl-4-phenyl-4-carbethoxyazacyclooctane (VI), we have also prepared α-1,3-dimethyl-4-phenyl-4-propionoxyazacyclooctane (XVII), which is an eight-membered ring analog of alphaprodine, a more potent analgesic than either ethoheptazine or meperidine.[5]

Formation of the azacyclooctane ring was ac-

(1) Taken in part from the dissertation of J. Diamond, submitted to the Temple University Graduate Council in partial fulfillment of the requirements for the degree of Doctor of Philosophy (1955).

(2) (a) Present address: Lincoln Laboratories, Decatur, Ill. (b) Wyeth Institute for Medical Research, Philadelphia 1, Pa. (c) Department of Chemistry, Temple University, Philadelphia 22, Pa.

(3) The generic name for 1-methyl-4-phenyl-4-carbethoxyazacycloheptane, also known as Zactane®. J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Org. Chem.*, 22, 399 (1957); J. Diamond and W. F. Bruce, U. S. Patent 2,666,050 (1954) [*Chem. Abstr.*, 49, 4031 (1955)]; F. F. Blicke and E.-P. Tsao, *J. Am. Chem. Soc.*, 75, 5587 (1953).

(4) J. Seifter, D. K. Eckfeld, I. A. Letchack, E. M Gore, and J. M. Glassman, *Federation Proc.*, 13, 403 (1954); A. J. Grossmann, M. Golbey, W. C. Gittinger, and R. C Batterman, *J. Am. Geriatrics Soc.*, 4, 187 (1956).

(5) The synthesis of an azacycloheptane analog of α-prodine will be reported in a subsequent paper.

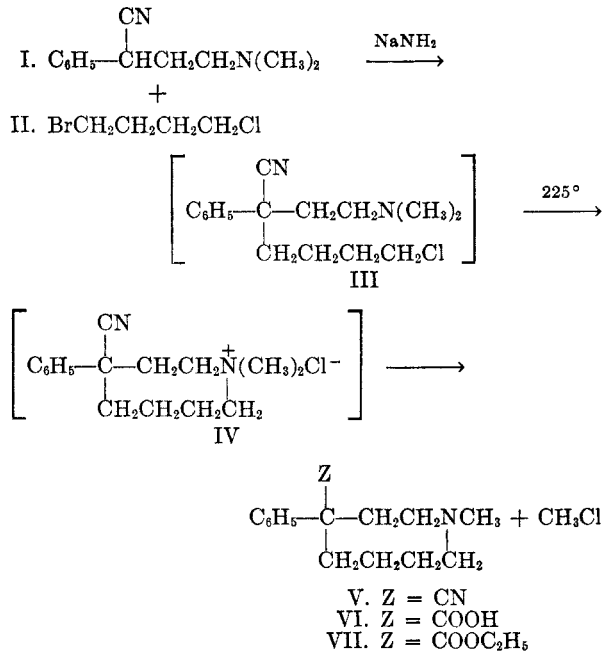


Figure 1

complished in the one case, as shown in Fig. 1, by first treating 2-phenyl-4-dimethylaminobutyronitrile (I) with tetramethylene chlorobromide (II). The sodio derivative of I, formed with sodamide, reacted with II in ether at −20° to −25° to produce 1-dimethylamino-3-phenyl-3-cyano-7-chloroheptane (III) which, because of its tendency to react with another molecule of itself, was not isolated. Upon heating a solution of this compound in 2,6,8-trimethylnonanol-4 at 225°, cyclization and dechloromethylation occurred to produce 1-methyl-4-phenyl-4-cyanoazacyclooctane (IV) in 21.9% over-all yield from I. This is half the yield obtained in the preparation of the nitrile in the seven-membered ring series by a similar process, no doubt a consequence of the less ready formation of eight-membered rings.

The direct conversion of III to V was resorted to after several unsuccessful attempts were made to cyclize III in nitrobenzene to the isomeric azacyclooctane quaternary salt IV. By contrast, a seven-membered ring quaternary salt was readily obtained in yields of 65–80% in this solvent by an analogous synthesis.[3]

Hydrolysis of the azacyclooctane nitrile (V) with 80% sulfuric acid at 115–120° produced the carboxylic acid (VI) which was not isolated, but was converted to VII by esterification with ethanol in the presence of sulfuric acid.

The eight-membered ring structures for V and VII were assigned on the basis of the elemental analyses, C-methyl values and molar refraction measurements. The C-methyl values, determined by the method of Kuhn and Roth,[6] confirmed the absence of a C-methyl group in the nitrile (V) and the presence of only one C-methyl group in the ester (VII). All isomeric contracted ring structures, such as VIII and IX, containing an extranuclear C-methyl group were thereby ruled out. Alicyclic structures X and XI were eliminated as a result of elementary analyses and molecular refraction (Fig. 2).

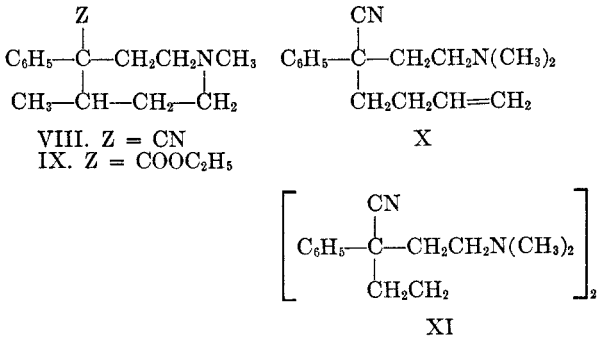


Figure 2

The preparation of XVII was accomplished, as shown in Fig. 3, by condensing methyl methacrylate (XII) with methylamine to give methyl ω-methylaminoisobutyrate (XIII).[7] By treating XIII with 5-chlorovaleronitrile in *n*-butyl ether at 110–115° over potassium carbonate for 16 hr. a new tertiary amine, 4-cyanobutyl-2-carbomethoxypropylmethylamine (XIV) resulted. Upon reaction of this compound in tetralin with sodium hydride at 150° for 1.5–2 hr. followed by hydrolysis and decarboxylation, without isolation of the intermediates, a keto tertiary amine (XV) was obtained which on analysis had the composition of 1,3-dimethylazacyclooctanone-4. The ketone function in this compound was shown upon its conversion by phenyllithium to a phenylaminocarbinol (XVI). Esterification with propionic anhydride gave the propionate (XVII).

A pharmacological evaluation of VII with ethoheptazine and meperidine showed that the analgesic potency of the new compound is considerably less than that of the others, coupled with increased toxicity. Study of XVII is not yet completed.[8]

EXPERIMENTAL[9]

1-Methyl-4-phenyl-4-cyanoazacyclooctane (V). A solution of 141 g. (0.75 mol.) of 2-phenyl-4-dimethylaminobutyronitrile[10] in 300 ml. of ether was added dropwise to 35.1 g. (0.90 mol.) of sodamide suspended in 700 ml. of anhydrous ether. The reaction was conducted at 30–35° with stirring under a nitrogen atmosphere. The mixture was then heated at its reflux temperature for 2 hr., cooled to −30°, and a solution of 153 g. (0.89 mol.) of tetramethylene chlorobromide in 300 ml. of ether was added dropwise at −25 to −20°. Upon completing the addition, the mixture was al-

(6) R. Kuhn and H. Roth, *Ber.*, **66**, 1274 (1933).

(7) D. R. Howton, *J. Org. Chem.*, **10**, 277 (1945).

(8) J. Seifter, private communication.

(9) All melting points were determined in an oil bath and are uncorrected; microanalyses by Dr. G. Ellis and associates.

(10) C. E. Kwarther and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946).

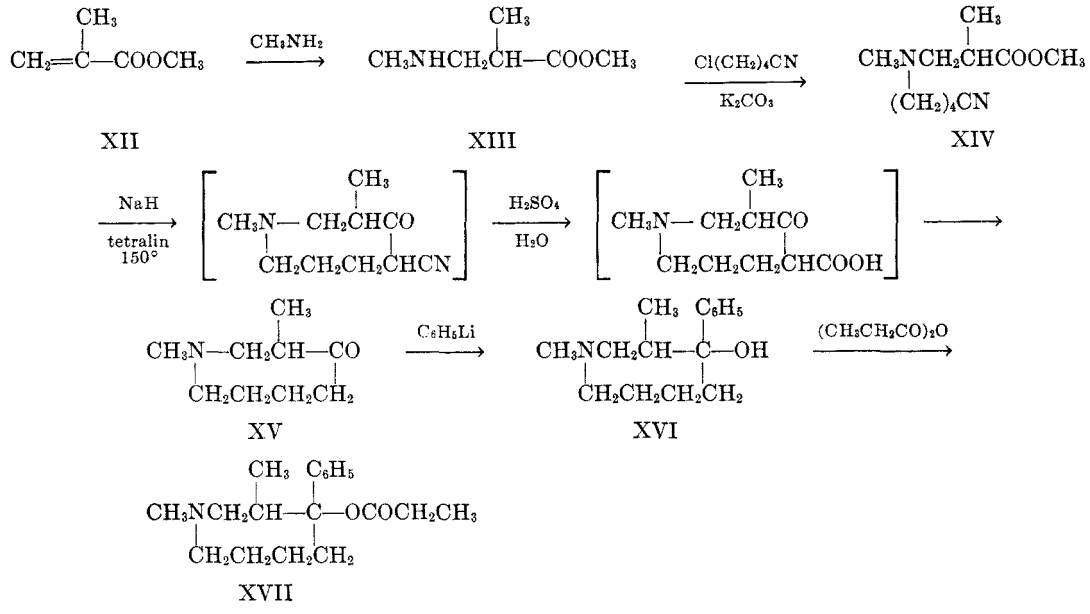


Figure 3

lowed to warm to room temperature and stand overnight. The precipitated inorganic salts were filtered off and the ether removed from the filtrate under reduced pressure. The liquid residue contained 1-dimethylamino-3-phenyl-3-cyano-7-chloroheptane (III).

One liter of 2,6,8-trimethylnonanol-4 was added to the residue and the solution added with stirring during 1.5 hr. to 1 l. of refluxing trimethylnonanol, b.p. 225°. The solution was heated at its reflux temperature for an additional 2 hr., then cooled under nitrogen and extracted with dilute hydrochloric acid. The acid extract was washed with ether, made alkaline with aqueous sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and the ether distilled off. The product was rapidly distilled away from a large quantity of resinous material at 140–160° at 0.3–0.4 mm. Redistillation of the crude material gave 37.4 g. (21.9%) of V, pale yellow liquid, b.p. 130–134° at 0.3 mm.; n_D^{27} 1.5270; d_4^{27} 1.010.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.82; N, 12.75; C—CH_3, 0.00; M_D 69.54. Found: C, 79.06; H, 9.32; N, 12.57; C—CH_3, 0.00; M_D 69.48.

The *picrate*, m.p. 158–159°, was formed in acetone-methanol.

Anal. Calcd. for $C_{21}H_{23}N_5O_7$: C, 55.18; H, 5.07; N, 15.32. Found: C, 55.33; H, 4.89; N, 15.13.

1-Methyl-4-phenyl-4-carbethoxyazacyclooctane (VII). A mixture of 9.1 g. (0.04 mol.) of V, 10.6 g. of 98% sulfuric acid, and 2.6 g. of water was heated at 115–125° for 3 hr. The resulting sirupy solution which contained 1-methyl-4-phenyl-4-carboxyazacyclooctane (VI) was cooled somewhat and 75 ml. of absolute ethanol added. After refluxing this solution for 16 hr., the excess ethanol was distilled off at atmospheric pressure. The cooled residue was poured slowly into an ice-cold saturated solution of sodium carbonate, and extracted with ether. Distillation of the dried and filtered extract gave 5.2 g. (46.9%) of VII, a colorless liquid, b.p. 130–133° at 0.3 mm.; n_D^{26} 1.5215; d_4^{26} 1.042. In a second reaction using 27.3 g. of V, 15.5 g. (45.9%) of VII was also obtained.

Anal. Calcd. for $C_{17}H_{25}N_2$: C, 74.18; H, 9.15; N, 5.08; C—CH_3, 5.46; M_D 80.70. Found: C, 74.07; H, 9.06; N, 4.99; C—CH_3, 5.59; M_D 80.68.

The *methiodide*, m.p. 165–167° dec., was formed in acetone-ether.

Anal. Calcd. for $C_{18}H_{28}INO_2$: C, 51.82; H, 6.76; N, 3.36; I, 30.5. Found: C, 51.92; H, 6.86; N, 3.09; I, 30.5.

4-Cyanobutyl-2-carbomethoxypropylmethylamine (XIV). Methyl β-methylaminoisobutyrate (XIII), boiling from 115–125° at 150 mm., n_D^{28} 1.4200, was prepared in 39% yield by the method of Howton,[7] except that the reaction mixture was worked up after standing overnight instead of 3 days. A mixture of 100 g. (0.85 mol.) of ω-chlorovaleronitrile, 111.5 g. (0.85 mol.) of XIII, and 120 g. (0.87 mol.) of anhydrous potassium carbonate in 300 ml. of *n*-butyl ether was stirred and heated at 110–115° for 16 hr. The solid was collected on a filter and was washed with ether. The filtrate was extracted three times with dilute hydrochloric acid. The combined acid extracts were washed with ether to remove traces of neutral material, then made alkaline with sodium hydroxide and extracted with ether. This extract was dried over anhydrous potassium carbonate, filtered, concentrated, and distilled to give 70.0 g. (39%) of XIV, a colorless liquid boiling from 117–122° at 0.20 mm., n_D^{24} 1.4465.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.20; H, 9.49; N, 13.20. Found: C, 62.41; H, 9.46; N, 13.31.

1,3-Dimethylazacyclooctanone-4 (XV). A mixture of 6.2 g. (0.125 mol.) of a 48.6% dispersion of sodium hydride in mineral oil and 350 ml. of tetralin was placed under nitrogen in a 1-l. 3-necked flask. After dropwise addition of 25.9 g. (0.122 mol.) of XIV to this mixture, stirring and heating at 150° was carried on for 2 hr., during which time the gray mixture became rose colored. Heating was discontinued and when the mixture had cooled somewhat, 10 ml. of methanol was added to destroy any unreacted sodium hydride. The mixture was then washed with water and with 100 cc. of 50% sulfuric acid. The acid extract was refluxed for 15 hr., during which time carbon dioxide evolution gradually decreased to zero. After the acid solution was cooled, diluted with an equal volume of water, and extracted with ether to remove neutral by-products, the product was obtained upon making the solution basic by adding 40% sodium hydroxide and extracting it with ether. After drying the ether over anhydrous potassium carbonate, filtering, concentrating, and distilling the product, 2.0 g. (10.5%) of a colorless liquid (XIV) boiling from 110–118° at 38–40 mm. was obtained.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.60; H, 11.03; N, 9.03. Found: C, 69.64; H, 10.89; N, 9.24.

α-1,3-Dimethyl-4-phenyl-4-propionoxyazacyclooctane (XVII). To a solution of phenyllithium prepared by adding 7.1 g. of bromobenzene to a mixture of 0.635 g. (0.091 g.-atom) of lithium shot and 50 ml. of anhydrous ether under nitrogen, followed by 2 hr. of reflux, was added at −20°, 2.0 g. (0.0129 mol.) of XIV in 25 ml. of toluene. After 0.5 hr., the reaction mixture was warmed to room temperature and allowed to stand overnight. A solution of 6.66 g. (0.0475 mol.) of propionic anhydride in 25 ml. of toluene with 2 drops of concentrated sulfuric acid as a catalyst was added and the solution was concentrated until the temperature of the distillate reached 105°, when the temperature was held at this point for 3 hr. After the solution was cooled and made alkaline by adding 20 ml. of 5% sodium hydroxide solution, the product was extracted from the toluene layer by washing with dilute hydrochloric acid, the acid extract washed with ether to remove traces of neutral material, and made alkaline by adding cold 4*N* sodium hydroxide. The product was taken up in ether, dried over anhydrous potassium carbonate, filtered, concentrated, and distilled to give 1.0 g. (27%) of amber liquid (XVII) boiling from 90–92° at 0.20 mm., n_D^{24} 1.5262. While two DL mixtures are possible, no evidence for more than one form, designated α, has been found in this product.

Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.41. Found: C, 74.88; H, 9.76.

The *picrate*, melting at 128–130°, was formed in ether and was recrystallized from 1-butanol.

Anal. Calcd. for $C_{24}H_{30}N_4O_9$: C, 55.60; H, 5.85; N, 10.80. Found: C, 55.73; H, 5.49; N, 10.41.

The *acid citrate*, melting at 134–135°, was formed in absolute ethanol.

Anal. Calcd. for $C_{24}H_{35}NO_9$: C, 59.90; H, 7.31; N, 2.91. Found: C, 60.97; H, 7.13; N, 2.98.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

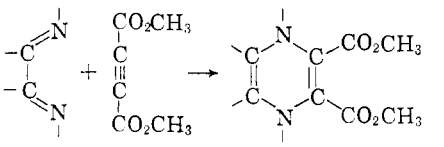
Reaction of 2-Phenylquinoxaline and of 2,3-Diphenylquinoxaline with Dimethyl Acetylenedicarboxylate[1]

ERLING GROVENSTEIN, JR., WILLIAM POSTMAN, AND JAMES W. TAYLOR

Received June 26, 1959

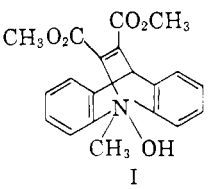
2,3-Diphenylquinoxaline reacts with dimethyl acetylenedicarboxylate in methanol to give a yellow product which consists of 1 mole each of 2,3-diphenylquinoxaline, dimethyl acetylenedicarboxylate, and methanol. On the basis of its reactions and ultraviolet absorption spectra, this product is assigned the structure 1-(1,2-dicarbomethoxyvinyl)-2,3-diphenyl-2-methoxy-1,2-dihydroquinoxaline (IV) in neutral or basic solution in methanol, while in acidic methanol it exists as 1-(1,2-dicarbomethoxyvinyl)-2,3-diphenylquinoxalinium cation (VI). 2-Phenylquinoxaline reacts similarly with dimethyl acetylenedicarboxylate to give a product which after long exposure to the atmosphere was isolated as 1-(1,2-dicarbomethoxyvinyl)-3-phenyl-2-hydroxy-1,2-dihydroquinoxaline (VIII). Reaction of 2,3-diphenylquinoxaline with hydrogen peroxide in acetic acid gave under the present conditions *N,N'*-dibenzoyl-*o*-phenylenediamine in addition to the previously reported *N,N'*-dioxo-2,3-diphenylquinoxaline.

The addition of dienophiles to 1-aza- and 1,4-diaza-1,3-dienes might be expected to occur in a manner analogous to the ordinary Diels-Alder reaction, thus for a 1,4-diaza-1,3-diene with dimethyl acetylenedicarboxylate as indicated in Equation 1. Such reactions, however, generally



(1)

appear to proceed in other ways if reaction occurs at all.[2] However, dehydroindigo undergoes 1,4-addition of dienophiles such as styrene to its two heterocyclic nitrogens[3] and acridine adds dimethyl acetylenedicarboxylate in methanol, according to Diels and Thiele,[4] to give chiefly an adduct which was formulated as stucture I. The report of Diels and Thiele encouraged us to investigate the reaction of dimethyl acetylenedicarboxylate with 2-phenyl- and 2,3-diphenylquinoxaline. During the course of the present work, Acheson and Burstall[5] showed that the product of Diels and Thiele had structure IIa in neutral



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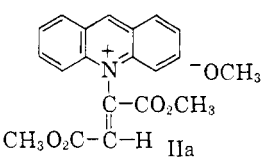
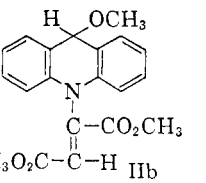


IIa



IIb

(1) Based chiefly upon the following theses at the Georgia Institute of Technology: W. Postman, Ph.D. Thesis, June, 1953; J. W. Taylor, M.S. thesis, June, 1958.

(2) M. C. Kloetzal, *Org. Reactions*, **4**, 1 (1948); H. L. Homes, *Org. Reactions*, **4**, 60 (1948).

(3) R. Pummerer, H. Fiesselmann, and O. Müller, *Ann.*, **544**, 206 (1940); R. Pummerer and E. Stieglitz, *Ber.*, **75**, 1072 (1942).

(4) O. Diels and W. E. Thiele, *Ann.*, **543**, 79 (1940).

(5) R. M. Acheson and M. L. Burstall, *J. Chem. Soc.*, 3240 (1954).