[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

Condensation of Dialdehydes with Reissert Compounds. Synthesis of a Compound Having Curariform Activity

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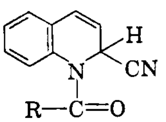
Received July 19, 1960

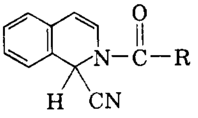
Reaction of two equivalents of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile with one equivalent of terephthalaldehyde gave both the *meso* form and racemate of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol. The respective diols were obtained by saponification of the esters, and each diol gave the same ketone, α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-dione, on chromic acid oxidation. The dione was converted to α,α'-bis(2-quinolyl)-*p*-xylylene by a Wolff-Kishner reduction. Treatment of the latter compound with methyl iodide gave α,α'-bis(2-quinolyl)-*p*-xylylene dimethiodide, which was found to be a moderately potent peripheral blocking agent that affects both neuromuscular and ganglionic transmission.

Reaction of two equivalents of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with one equivalent of terephthalaldehyde gave both the *meso* form and racemate of *O,O*-dibenzoyl-α,α'-bis(1-isoquinolyl)-*p*-xylylene-α,α'-diol. One of the diastereoisomers of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*o*-xylylene-α,α'-diol was obtained by treatment of phthalaldehyde with the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile.

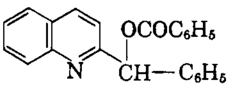
Reissert compounds, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) are easily converted to the respective lithium salts in exchange reactions with phenyllithium, and the salts, in turn, readily undergo condensation reactions with a variety of electrophilic reagents. The reactions of the lithium salts with aldehydes, in particular, take place rapidly and give high yields of condensation-rearrangement products.[1] For example, the reaction of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile (R = C_6H_5) with benzaldehyde gives phenyl-2-quinolylcarbinyl benzoate (III) in 89% yield.



I

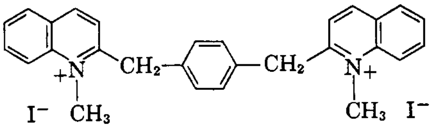


II

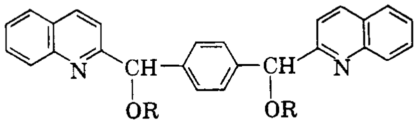


III

With the ultimate objective in mind of preparing α,α'-bis(2-quinolyl)-*p*-xylylene dimethiodide (IV) as a possible curariform agent, we decided to investigate the reaction of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5) with terephthaladehyde. Condensation of two equivalents of the salt with one of the aldehyde gave two products of the molecular formula $C_{40}H_{28}N_2O_4$, the one of m.p. 258.5–259.5° in 80% yield and the other of m.p. 209–210° in 8% yield. These products, the infrared spectra of which were found to be identical, are undoubtedly the racemic and *meso* forms of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = COC_6H_5), but no attempt was made to distinguish one from the other inasmuch as the centers of asymmetry were eventually eliminated in the conversion of these esters to IV.

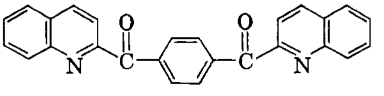


IV



V

Saponification of the diester V (R = COC_6H_5) of m.p. 258.5–259.5° gave α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = H) of m.p. 193–196°. In a similar saponification reaction of the diester of m.p. 209–210°, a diol of m.p. 179–184° was obtained. The somewhat large melting point ranges of the two diols suggest that partial interconversion of the *meso* and racemic forms occurred under the alkaline conditions of hydrolysis. This was not unexpected inasmuch as the side chain hydrogen atoms of quanaldine and its derivaties are known to be acidic. Oxidation of each of the two samples of the diol V (R = H) with chromic acid gave the same diketone, α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-dione (VI), thus confirming the supposition that the two diesters (V. R = COC_6H_5) and the two diols diols (V R = H) were diastereoisomeric pairs. The saponification reactions and oxidation reactions gave the products cited above in yields of 98% and 93%, respectively.



VI

α,α'-Bis(2-quinolyl)-*p*-xylylene was obtained from VI in quantitative yield by application of the Huang-Minlon modification of the Wolff-Kishner reduction. Treatment of α,α'-bis(2-quinolyl)-*p*-xylylene with methyl iodide in a Parr bomb at an

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[1] L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, 80, 1177 (1958).

elevated temperature gave the dimethiodide IV in 98% yield.

As an extension of the scope of the condensation-rearrangement reaction of Reissert compounds with aldehydes, two equivalents of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile were caused to react with one equivalent of terephthalaldehyde, and both the racemic and *meso* forms of *O,O*-dibenzoyl-α,α'-bis(1-isoquinolyl)-*p*-xylylene-α,α'-diol were isolated. One isomer of m.p. 208–209° was obtained in 83% yield and the other of m.p. 228–230° in 8% yield. One of the diastereoisomers of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*o*-xylylene-α,α'-diol, m.p. 226.5–227.5°, was obtained in low yield following the condensation of two equivalents of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile with one equivalent of phthalaldehyde.

Pharmacological testing. α,α'-Bis(2-quinolyl)-*p*-xylylene dimethiodide (IV) was found to be a moderately potent peripheral blocking agent that affects both neuromuscular and ganglionic transmission. It probably should be classed as competitive rather than depolarizing in its action. By usual definitions the median curarizing and ganglionic blocking dose might be estimated at 4 or 5 mg/kg. i.v.[2]

EXPERIMENTAL[3]

1-Benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5). This compound was prepared by the method of Rupe, Paltzer, and Engel.[4]

2-Benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5). The method of Padbury and Lindwall[5] was used for the preparation of this compound.

Phenyllithium. Freshly prepared phenyllithium, made by the method of Gilman,[6] was used for each experiment. The lithium bromide formed in the reaction was not removed.

O,O-Dibenzoyl-α,α'-bis(2-quinolyl)-p-xylylene-α,α'-diol (V. R = COC_6H_5). To a solution of 10.4 g. (0.04 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5) in 150 cc. of anhydrous ether and 75 cc. of anhydrous dioxane maintained at −10° in an atmosphere of pure nitrogen was added with mechanical stirring an ether solution of 0.04 mole of freshly prepared phenyllithium. To the resulting red solution there was added dropwise with stirring a solution of 2.68 g. (0.02 mole) of terephthalaldehyde in 20 cc. of anhydrous dioxane. As the addition of aldehyde progressed the color faded slowly, and, on completion of the addition, the color was light pink. The mixture was stirred for 2 hr. at −10°, warmed to room temperature and stirred for an additional 4 hr. The reaction mixture was filtered and the solid washed well with water until the washings were no longer basic to litmus. After the solid had been dried for an extended period, it amounted to 9.6 g. (80% yield) of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = COC_6H_5), m.p. 228–235°. Recrystallization from anhydrous benzene-petroleum ether (b.p. 60–110°) yielded a white solid melting at 258.5–259.5°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.90; H, 4.97; N, 4.86.

The organic phase, after collection of the above mentioned solid, was evaporated to dryness, yielding a yellow solid. After having been washed well with hot 95% ethanol and dried, the remaining white solid, 0.80 g., melted at 203–216°. From the ethanol wash an additional 0.16 g. of material melting at 199–204° was obtained. The total yield (0.96 g.) of this material, presumed to be the diastereoisomer of the compound cited above, was 8%. Two recrystallizations from acetone yielded a solid melting at 209–210°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 80.21; H, 4.62; N, 4.64.

The infrared spectra of the compounds melting at 258.5–259.5° and 209–210°, respectively, taken in potassium bromide pellets, were found to be identical.

O,O-Dibenzoyl-α,α'-bis(1-isoquinolyl)-p-xylylene-α,α'-diol. These compounds, derived from 2-benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5) and terephthalaldehyde as starting materials, were synthesized in the same manner as that described above for the preparation of the corresponding quinoline compounds. Filtration of the colorless reaction mixture followed by a thorough washing and drying of the precipitate yielded 10.0 g. (83% yield) of *O,O*-dibenzoyl-α,α'-bis(1-isoquinolyl)-*p*-xylylene-α,α'-diol, m.p. 160–195°. Several recrystallizations from acetone yielded a white solid melting at 208–209°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.86; H, 4.80; N, 4.95.

As in the preceeding experiment, there was obtained from the organic phase 0.98 g. (8% yield) of a white solid, melting point 215–224°, believed to be the diastereoisomer of the compound of m.p. 208–209°. Two recrystallizations from ethanol-water yielded a sample of m.p. 228–230°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.87; H, 4.63; N, 4.78.

The infrared spectra of the compounds melting at 208–209° and 228–230°, respectively, taken in potassium bromide pellets, were found to be identical.

α,α'-Bis(2-quinolyl)-p-xylylene-α,α'-diol (V. R = H). The first sample of this compound was prepared by saponification of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = COC_6H_5) of m.p. 258.5–259.5°. A suspension of 5.0 g. of the dibenzoate ester in 130 cc. of ethanol was mixed with a solution of 5.0 g. of potassium hydroxide in 30 cc. of water, and the resulting mixture was refluxed for 9 hr. The bulk of the ethanol was removed under an air-jet, and the residue was mixed with 100 cc. of water. The solid was collected by filtration and washed with water until the washings were free of base. There was obtained 3.23 g. (98% yield) of α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = H), m.p. 190–200°. After several recrystallizations from acetone the m.p. was 193–196°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.56; H, 5.14; N, 7.14. Found: C, 79.62; H, 5.24; N, 7.08.

Saponification of the diastereoisomeric ester, m.p. 209–210°, in the same manner yielded a solid, which, after several recrystallizations from an ethanol-water mixture, melted at 179–184°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.56; H, 5.14; N, 7.14. Found: C, 79.40; H, 5.36; N, 7.25.

The infrared spectra of the two diols, taken in potassium bromide pellets, were found to be identical.

α,α'-Bis(2-quinolyl)-p-xylylene-α,α'-dione (VI). A solution of 3.30 g. (0.0111 mole) of sodium dichromate in 15 cc. of glacial acetic acid maintained at 16° was slowly added to a suspension of 6.00 g. (0.0153 mole) of α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = H), m.p. 193–196°, in acetic acid. The yellow solid which formed initially gradually underwent a change to a gray-blue color as the reaction mixture was slowly heated to 60°. At this point the mixture was allowed to come to room temperature, then it was filtered

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[2] We are indebted to Dr. Dwight D. Morrison of the Eli Lilly Co. who made the arrangements for the testing of this compound.

[3] All melting points are corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

[4] H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).

[5] J. J. Padbury and J. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

[6] H. Gilman, *J. Am. Chem. Soc.*, **55**, 1262 (1933).

and the precipitate washed well with water. There was obtained 5.50 g. (93% yield) of α,α′-bis(2-quinolyl)-*p*-xylylene-α,α′-dione (VI) m.p. 282–284°. After several recrystallizations from acetone the compound melted at 283.5–284.5°.

Anal. Calcd. for $C_{26}H_{16}N_2O_2$: C, 80.39; H, 4.15; N, 7.21. Found: C, 80.16; H, 4.37; N, 7.07.

In a similar fashion, oxidation of the diastereoisomeric diol of m.p. 179–184° yielded a white solid of m.p. 282–284°. A mixed melting point test with the analyzed sample of α,α′-bis(2-quinolyl)-*p*-xylylene-α,α′-dione (VI) obtained by the oxidation of the diol of m.p. 193–196° showed no depression. The infrared spectra, taken in potassium bromide pellets, of the two samples of the oxidation product were found to be identical.

α,α′-Bis(2-quinolyl)-p-xylylene. A mixture of 5.78 g. (0.0149 mole) of α,α′-bis(2-quinolyl)-*p*-xylylene-α,α′-dione (VI), 40 cc. of 85% hydrazine and 150 cc. of triethyleneglycol was refluxed for 2 hr. The initially white solid gradually changed to yellow. Excess hydrazine and water were evaporated by heating the mixture under an air-jet, and the temperature was raised to about 220°. Addition of about 5.0 g. of potassium hydroxide caused a vigorous reaction to ensue, one terminating in the formation of a golden brown solution. The solution was heated at 220° for 1 hr., then allowed to cool slowly to room temperature. Approximately 100 cc. of water was added to the solution causing formation of a crystalline solid. The solid, α,α′-bis(2-quinolyl)-*p*-xylylene, after filtration and drying, weighed 5.31 g. (quantitative yield) and melted at 132–135°. Recrystallization from an ethanol-water mixture yielded needle-like crystals of m.p. 135–136°.

Anal. Calcd. for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59; N, 7.77. Found: C, 86.70; H, 5.50; N, 7.85.

α,α′-Bis(2-quinolyl)-p-xylylene dimethiodide (IV). A Parr bomb was charged with 1.0 g. (0.0028 mole) of α,α′-bis(2-quinolyl)-*p*-xylylene and 12 g. of methyl iodide and heated for 9 hr. at 75°. After evaporation of the excess methyl iodide under vacuum there was obtained 2.30 g. of a yellow-green solid decomposing at 273°. The solid was dissolved in boiling water and hydrogen iodide solution was added until the solution was acidic. After filtration of the hot solution, the filtrate, on cooling, yielded 1.71 g. (98% yield) of a yellow solid, α,α′-bis(2-quinolyl)-*p*-xylylene dimethiodide (IV), melting with decomposition at 289–292°.

Anal. Calcd. for $C_{28}H_{26}N_2I_2$: C, 52.19; H, 4.07; N, 4.35; I, 39.39. Found: C, 52.23; H, 4.45; N, 4.50; I, 39.22.

O,O-Dibenzoyl-α,α′-bis(2-quinolyl)-o-xylylene-α,α′-diol. The lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile was treated with phthalaldehyde in the same manner as that described for the preparation of the *p*-xylylene compounds. Addition of 20 cc. of water to the reaction mixture resulted in complete solution of the solid. The organic layer was separated, washed with three 10-cc. portions of water, dried over anhydrous magnesium sulfate, and evaporated to yield a reddish oil. Subjection of the oil to vacuum treatment for several days failed to induce complete solidification. In an attempt to recrystallize the gum (weight 10.77 g.) from 95% ethanol, a slight amount of a light yellow solid was found to be insoluble. After it had been collected by filtration, the solid weighed 1.50 g. and melted at 217–221°. Recrystallization from a benzene-petroleum ether mixture (b.p. 60–110°) yielded a solid which melted at 226.5–227.5°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.76; H, 4.84; N, 4.97.

Acknowledgment. This investigation was supported by a research grant, E-1961, from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service.

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CONTRIBUTION FROM THE CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis and Biological Properties of 4-Amino-5-isopropyl-3-isoxazolidone, a Substituted Cycloserine

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Received August 12, 1960

α-Bromo-β-hydroxy-γ-methylpentanoic acid was treated with ammonium hydroxide to yield the desired α-amino acid which was then esterified in the presence of anhydrous hydrogen chloride with ethanol. The β-hydroxy grouping was subsequently replaced by chlorine and the resulting ethyl α-amino-β-chloro-γ-methylpentanoate was finally treated with hydroxylamine and cyclized to yield 4-amino-5-isopropyl-3-isoxazolidone (I). I is inhibitory to the growth of *Leuconostoc dextranicum* when this organism is grown in a medium containing D-leucine as the exogenous source of this required metabolite; however, I is essentially not toxic for *L. dextranicum* when it is grown on media containing DL-leucine. It appears that appropriately substituted cycloserine derivatives may specifically inhibit D-amino acid functions.

Cycloserine (D-4-amino-3-isoxazolidone)[2a] was originally isolated from culture filtrates of streptomycetes[2b] and its chemical structure was subsequently established.[3,4] It is an antibiotic which has been found effective in a number of microbial systems.[5] Metabolic studies with this compound have demonstrated it to be a competitive antagonist of D-alanine in preventing the incorporation of D-alanine into a uridine nucleotide intermediate

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[1] Rosalie B. Hite postdoctoral fellow, 1959–1960.

(2)(a) Oxamycin, Merck and Co., Inc.

(2)(b) For references see *Antibiotics, Their Chemistry and Non-Medical Uses*, ed. H. S. Goldberg, Van Nostrand, New York, 1959, p. 71.

(3) F. A. Kuehl, F. J. Wolf, N. R. Trenner, R. L. Peck, E. Howe, B. D. Hunnewell, G. Dowing, E. Newstead, R. P. Buhs, I. Putter, R. Ormond, J. E. Lyons, L. Chaiet, and K. Folkers, *J. Am. Chem. Soc.*, 77, 2344 (1955).

(4) P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz, and H. R. Sullivan, *J. Am. Chem. Soc.*, 77, 2345 (1955).

(5) E. B. Chain, *Ann. Rev. Biochem.*, 27, 167 (1958).