[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

A New Method for the Synthesis of Certain Benz[a]acridines[1]

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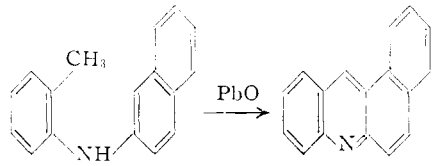
RECEIVED FEBRUARY 17, 1955

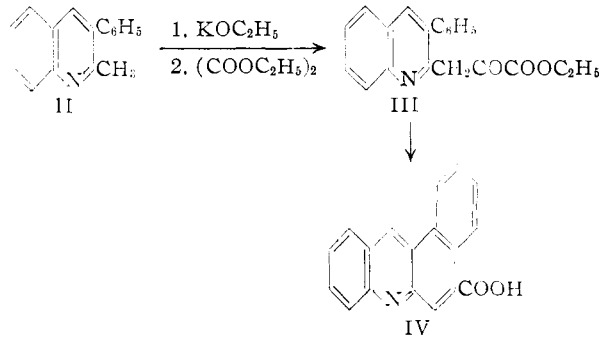
Certain 5-substituted benz[a]acridines were synthesized by acylating the methyl group of 3-phenylquinaldine or a derivative with an ester, and cyclizing the resulting ketone. The cyclizations were effected with polyphosphoric acid.

Benz[a]acridine (I) and its derivatives have generally been synthesized by condensations between appropriately substituted benzenes and naphthalenes in which the pyrido-portion of the benzacridine molecule is formed.[2] For example, I was originally synthesized by the cyclization of *o*-tolyl-2-naphthylamine which was prepared from *o*-toluidine hydrochloride and 2-bromonaphthylene.[3]



I

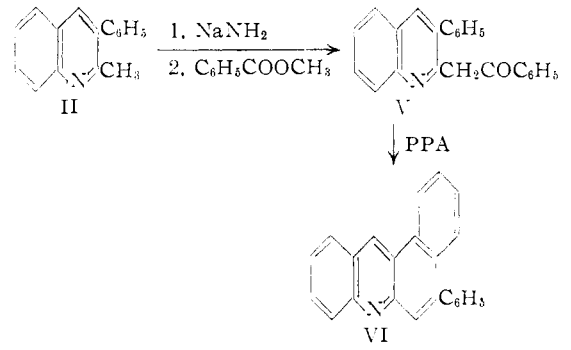
In the present investigation certain 5-substituted benz[a]acridines were prepared by the Claisen type of acylation of the methyl group of 3-phenylquinaldine (II) with an ester, and the aromatic cyclodehydration of the resulting quinaldyl ketone by means of polyphosphoric acid (PPA).[4] These two steps produced the final fused benzene ring of the benzacridine molecule. Thus, benz[a]acridine-5-carboxylic acid (IV) was obtained in 28% over-all yield from II and ethyl oxalate. The ethoxylation of II to form intermediate III was effected in 43% yield essentially as described previously[5]; this yield is probably not the maximum obtainable. The cyclization of III to form IV was realized in 66% yield. It was not determined whether the ester group was hydrolyzed during the cyclization or in the subsequent working up process. 3-Phenylquinaldine (II) was readily available through a Pfitzinger synthesis using isatin and phenylacetone, followed by decarboxylation.[5]



II III IV

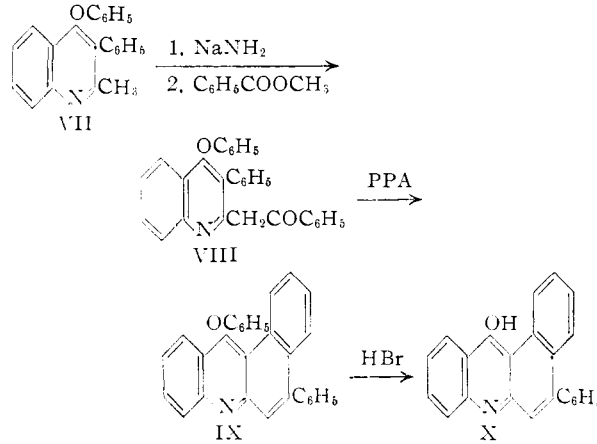
Acid IV was decarboxylated to form unsubstituted benz[a]acridine (I) which was identified by its melting point and ultraviolet spectra.[6]

Similarly 5-phenylbenz[a]acridine (VI) was obtained in 46% yield from 3-phenylquinaldine (II) and methyl benzoate. The benzoylation of II to form intermediate V was realized in 53% yield, and its cyclization to give VI, in 87% yield. The ultraviolet spectra of VI was similar to that of I although the presence of the 5-phenyl group caused a bathochromic shift of about 6 mμ.



II V VI

Also, 5-phenyl-12-phenoxybenz[a]acridine (IX) was obtained in 31% yield by benzoylating VII and cyclizing the resulting quinaldyl ketone. The yields in the 2 steps were 51 and 62%, respectively. The phenoxy derivative (IX) was cleaved with hydrobromic acid to form X which was converted to VI by means of zinc dust. The hydroxy derivative X was obtained more conveniently (in 50% yield from VIII) by treating the reaction mixture of VIII



VII VIII IX X

(1) Supported by the Eli Lilly Company and the Duke University Research Council.

(2) See A. Albert, "The Acridines," Edward Arnold and Co., London, 1951, p. 146; Ng. Ph. Buu-Hoi, R. Royer, M. Hubert-Habart and P. Mabille, *J. Chem. Soc.*, 3585 (1953); D. P. Spalding, E. C. Chapin and H. S. Mosher, *J. Org. Chem.*, **19**, 357 (1954).

(3) F. Ullmann and A. La Torre, *Ber.*, **37**, 2922 (1904).

(4) This reagent has been found particularly suitable for various cyclizations; see, for example, H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2962 (1950); J. Koo, *ibid.*, **75**, 1891 (1953). Recently, this reagent has been used by C. K. Bradsher and co-workers for certain aromatic cyclodehydrations in the biphenyl series to form phenanthrenes (private communication).

(5) W. Borsche and O. Vorbach, *Ann.*, **537**, 22 (1938).

(6) G. M. Badger, R. S. Pearce and R. Pettit, *J. Chem. Soc.*, 3202 (1951).

and polyphosphoric acid with hydrobromic acid. The starting phenoxy compound VIII was prepared in 60% yield by treating 2-methyl-3-phenyl-4-quinolinol with phosphorus oxychloride followed by sodium phenoxide, the quinolinol being readily available by the method described recently.[7]

It should be mentioned that the acylation of VII with methyl benzoate by means of sodium amide was apparently not accompanied by the displacement of the phenoxy group by the amide ion to form the amine.[8]

Experimental[9]

3-Phenylquinaldine (II).—This compound was prepared from 0.15 mole of phenylacetone and isatin in the presence of alkali essentially as described by Borsche and Vorbach[5] who reported the reaction on a 0.037 mole scale. The intermediate 2-methyl-3-phenylcinchoninic acid melted at 338° dec.; lit.[5] m.p. 312°. This acid was decarboxylated by heating 50 g. of it with 17 g. of copper powder in a flask at 340–350° for 2 hours (the flask first being placed in a Wood's metal bath at 250°). The reaction mixture was cooled, and stirred with benzene. After filtering, the solvent was removed, and the residue distilled *in vacuo* to give 35.4 g. (85%) of II as a yellow oil, b.p. 164° (1.7 mm.); lit.[5] b.p. 207–209° (12 mm.).

Ethyl (3-Phenyl-2-quinolyl)-pyruvate (III).—This compound was prepared from 0.065 mole each of 3-phenylquinaldine and ethyl oxalate in the presence of potassium ethoxide essentially as described by Borsche and Vorbach[5] except that the active hydrogen component was first mixed with the reagent and the ester then added. The product, obtained as orange needles after recrystallization from ethanol, melted at 161–163° dec.; lit. m.p. 160°.[5]

Benz[a]acridine-5-carboxylic Acid (IV).—A mixture of 1.0 g. of ethyl (3-phenyl-2-quinolyl)-pyruvate (III) and 10 g. of polyphosphoric acid[10] was heated in a test-tube on the steam-bath until most of the solid had dissolved and then on a metal bath at 195° for 15 minutes. After cooling to about 80°, the solution was stirred with 20 ml. of water until the polyphosphoric acid was decomposed, and the mixture then filtered. The solid was suspended in water, and the mixture neutralized with 20% sodium hydroxide. The resulting solid was collected on a funnel and triturated with hot 95% ethanol to give, after drying, 0.67 g. of yellow powder, m.p. 340° dec. Sublimation of 0.200 g. of this powder gave 0.165 g. of acid IV, m.p. 348° dec. The yield of pure IV from III was 65%.

Anal. Calcd. for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 79.11; H, 4.19; N, 5.00.

A sample (0.100 g.) of acid IV was decarboxylated by heating it with 0.1 g. of copper powder for 30 minutes at 340° in a sublimation tube. The resulting mixture was sublimed at 140° at 0.5 mm. forming 0.047 g. of yellow needles of benz[a]acridine (I), m.p. 132–133°, lit. m.p. 131°. After resublimation, it gave the ultraviolet absorption spectra reported for I.[6]

2-Phenacyl-3-phenylquinoline (V).—To a suspension of sodium amide (prepared from 3.45 g., 0.15 mole of sodium) in liquid ammonia was added a solution of 16.4 g. (0.075 mole) of 3-phenylquinaldine (II) in ether, and the resulting mixture stirred for 10 minutes. Methyl benzoate (9.6 g., 0.07 mole) in ether was added, and the mixture stirred for 4 hours allowing the ammonia to evaporate. After refluxing for 30 minutes, water was added, and the solid removed by filtration. More solid was recovered from the ether layer of the filtrate by distillation of the solvent, and the combined solids were recrystallized from ethanol giving 12.0 g. (53%) of orange needles of 2-phenacyl-3-phenylquinoline (V), m.p. 166–169°. A sample of this material was recrystallized from ethanol forming bright orange needles, m.p. 169–170°.

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.33; H, 5.26; N, 4.22.

5-Phenylbenz[a]acridine (VI).—One gram of 2-phenacyl-3-phenylquinoline (V) was treated with 20 g. of polyphosphoric acid essentially as described for the cyclization of III. After heating at 195° for 1.5 hours and decomposing with water, the mixture was neutralized with 20% sodium hydroxide and extracted with ether. The ether layer was washed with water, dried and the solvent removed. The residue was recrystallized from 95% ethanol to give yellow needles of 5-phenylbenz[a]acridine (VI). After drying thoroughly on the steam-bath, the product melted at 144–146°; yield 0.82 g. (87%). A sample was sublimed at 160° (0.4 mm.) and then recrystallized from 95% ethanol yielding yellow needles, m.p. 146–147° (after drying at 100°).

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.52; H, 4.90; N, 4.52.

The picrate of VI, after recrystallization from ethanol, was obtained as yellow needles, m.p. 289–290° dec.

Anal. Calcd. for $C_{29}H_{18}O_7N_4$: C, 65.17; H, 3.39; N, 10.48. Found: C, 64.80; H, 3.68; N, 10.53.

3-Phenyl-4-phenoxyquinaldine (VII).—2-Methyl-3-phenyl-4-quinolinol[7] was converted to its 4-chloro derivative by means of phosphorus oxychloride as described recently.[7] A mixture of 20 g. (0.08 mole) of 3-phenyl-4-chloroquinaldine, 9.3 g. of sodium phenoxide and 40 g. of phenol was refluxed for 4 hours. The resulting mixture was made strongly alkaline with 20% sodium hydroxide and extracted with ether. The solvent was removed from the ether extract, and the residue was washed with 20% sodium hydroxide and then with water. The solid was recrystallized from 95% ethanol yielding 19.8 g. (81%) of nearly colorless crystals of 3-phenyl-4-phenoxyquinaldine (VII), m.p. 123–126°. A sample, recrystallized from 95% ethanol, melted at 123–126°.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.89; H, 5.74; N, 4.32.

2-Phenacyl-3-phenyl-4-phenoxyquinoline (VIII).—A solution of 9.36 g. (0.03 mole) of 3-phenyl-4-phenoxyquinaldine (VII) in ether was added to a suspension of sodium amide (prepared from 1.38 g., 0.06 mole of sodium) in liquid ammonia, and the mixture stirred 5 minutes. Methyl benzoate (8.16 g., 0.06 mole) in ether was added, and the resulting mixture stirred for 1.5 hours. The ammonia was removed and the ether suspension refluxed for 8 hours. Water was added and the solid removed by filtration. More of the solid was isolated from the ether layer of the filtrate. The combined solids were recrystallized from ethanol yielding 6.4 g. (51%) of orange plates of 2-phenacyl-3-phenyl-4-phenoxyquinoline (VIII), m.p. 183–186°. A sample recrystallized from ethanol melted at 185.5–187°.

Anal. Calcd. for $C_{29}H_{21}NO_2$: C, 83.83; H, 5.09; N, 3.37. Found: C, 83.63; H, 5.29; N, 3.43.

5-Phenyl-12-phenoxybenz[a]acridine (IX).—Three grams of 2-phenacyl-3-phenyl-4-phenoxyquinoline (VIII) was treated with 30 g. of polyphosphoric acid essentially as described for the cyclization of III. After heating at 195° for 2.5 hours and decomposing with water, the solid was removed by filtration and suspended in 120 ml. of 1 *N* sodium hydroxide. This mixture was extracted with ether and the solvent was removed from the ether extract. The residue was recrystallized from 95% ethanol yielding 1.60 g. of light yellow 5-phenyl-12-phenoxybenz[a]acridine (IX), m.p. 204–207.5°. More of IX (0.18 g.), m.p. 202–206°, was isolated; total yield 62%. A sample of this compound, recrystallized from ethanol, melted at 207–209°.

Anal. Calcd. for $C_{29}H_{19}ON$: C, 87.63; H, 4.82; N, 3.52. Found: C, 87.26; H, 5.17; N, 3.43.

5-Phenylbenz[a]acridine-12(7)-one (X).—This compound (X) was prepared in the good yield by the hydrolysis of IX with hydrobromic acid. It was prepared more conveniently by hydrolyzing the crude solid obtained from the reaction of VIII with polyphosphoric acid. This solid (from 1.0 g. of VIII) was refluxed with a mixture of 5 ml. of 48% hydrobromic acid, 20 ml. of ethanol and 5 ml. of water for

(7) C. R. Hauser and J. G. Murray, THIS JOURNAL, **77**, 2851 (1955).

(8) Similarly 2-methoxy-4-methylquinoline has been benzoylated without displacing the methoxy group; C. R. Hauser and J. G. Murray, THIS JOURNAL, **77**, 2893 (1955). However, the methoxy group of 2-methoxyquinoline has been displaced by the amide ion to form 2-aminoquinoline in the presence of potassium amide in liquid ammonia at room temperature; F. W. Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).

(9) Melting and boiling points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

(10) We are indebted to The Victor Chemical Works, Chicago, Illinois, for a generous sample of this reagent.

3 hours (with stirring). The resulting mixture was neutralized with sodium hydroxide, and the solid removed by filtration. After washing thoroughly with water and ether and triturating with hot ethanol, X was obtained as a yellow solid (0.39 g., 50%), m.p. 330° dec. A sample, purified by sublimation, melted at 342° dec.

Anal. Calcd. for $C_{23}H_{15}ON$: C, 85.96; H, 4.71; N, 4.36. Found: C, 86.16; H, 4.74; N, 4.24.

A sample of this compound (0.25 g.) was heated with zinc dust (20 g.) to red heat in a combustion tube. The material, which distilled onto the walls of the tube, was resublimed at 160° (0.4 mm.), and recrystallized from ethanol, to give 5-phenylbenz[a]acridine, m.p. 146–146.5° (after drying at 100°). Admixture with VI (prepared above) gave no depression in the melting point.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

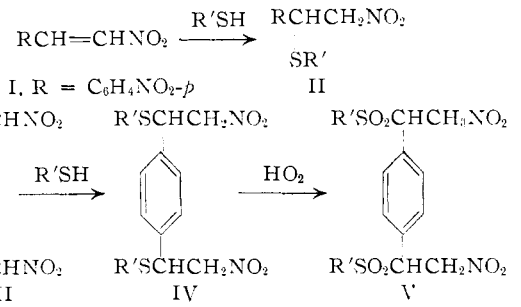
Reactions with Mercaptans. II.[1] Action of Aromatic Thiols on ω-Nitrostyrenes, 4-Styryl-5-oxazolones and 2-Phenyl-3,1-benzoxaz-4-one

BY AHMED MUSTAFA, ABDEL HAMID ELSAYED HARHASH AND MOHAMED KAMEL

RECEIVED SEPTEMBER 20, 1954

ω-Nitrostyrenes add aromatic thiols to give the β-nitrosulfides, which are oxidized readily to the β-nitrosulfones. The treatment of 4-styryl-5-oxazolones (VI and IX) with aromatic thiols resulted in opening of the hetero ring and addition to the double bond to yield VIII and X, respectively. Whereas, the hetero ring of benzo- and 3-benzoylbenzoxazol-2-one is stable toward aromatic thiols, that of 2-phenyl-3,1-benzoxaz-4-one (XI) is opened readily yielding the corresponding thioanthranilates (XII).

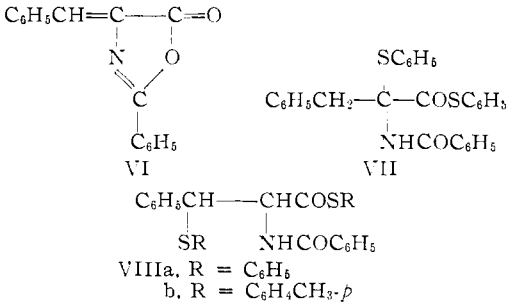
In conjunction with a study of the pharmacological action of sulfur-containing compounds against *Bilharziasis* snails,[2] the β-nitrosulfides (II and IV) were prepared by the addition of aromatic thiols to the ω-nitrostyrenes (I and III)[3] in the presence or absence of piperidine.[4]



The sulfides were oxidized to the corresponding sulfones (V) with hydrogen peroxide.[5] As the 1,4-addition of thiols to ω-nitrostyrene is established,[3] we have assigned structures II, IV and V, as indicated, to the β-nitrosulfides and sulfones prepared in this study, particularly since the reactions were not carried out under the influence of peroxides.[6]

The addition of mercaptans to the double bond of oxazolones of type VI, a reaction which has been extensively studied in connection with the synthesis of penicillamine, probably follows cleavage of the hetero ring.[7]

Ruhemann[8] has reported that thiophenol reacts with 2-phenyl-4-benzal-5-oxazolone (VI) to give the 2,1-addition product which he represented as VII. Under somewhat different conditions we have obtained the product described by Ruhemann. However, in view of the well-established mechanism for the addition of thiols to analogous α,β-unsaturated compounds (α,β-unsaturated ketones,[9] 1-cyano-1-cyclohexene[10] and alkylacrylonitriles[11]), this addition product of thiophenol and VI is probably VIIIa, β-phenylmercapto-β-phenyl-α-benzamidomonophenylthiopropionate, rather than VII.



Similarly, the treatment of VI with *p*-thiocresol caused opening of the hetero ring and addition to the double bond[12] to give VIIIb which was decomposed readily by alcoholic hydroxide[13] to give α-benzamidocinnamic acid and *p*-thiocresol. The acid was transformed readily to the oxazolone VI with acetic anhydride.

Terephthalylidene-bis-(2-phenyl-5-oxazolone) (IX) reacted with aromatic thiols in the presence of piperidine, in a manner similar to VI, to give the corresponding addition products X. The *p*-thiocresol addition product, on treatment with alcoholic potassium hydroxide, yielded *p*-thiocresol and an

(1) Part I: A. Mustafa, *J. Chem. Soc.*, 1370 (1951).

(2) M. O. Nolan, H. W. Bond and E. R. Mann, *Am. J. Trop. Med. and Hyg.*, **2** [4], 716 (1953).

(3) L. F. Cason and C. C. Wanser, THIS JOURNAL, **73**, 142 (1951); R. L. Heath and A. Lambert, *J. Chem. Soc.*, 1477 (1947).

(4) R. M. Ross, THIS JOURNAL, **71**, 3458 (1949).

(5) H. Gilman and N. J. Beaber, *ibid.*, **47**, 1450 (1925).

(6) S. O. Jones and E. E. Reid, *ibid.*, **60**, 2452 (1938); M. S. Kharasch, A. T. Read and F. R. Mayo, *Chemistry & Industry*, 752 (1938).

(7) H. T. Clarke, J. H. Johnson and R. Robinson, ed., "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 737.

(8) S. Ruhemann, *J. Chem. Soc.*, **87**, 468 (1905).

(9) T. Posner, *Ber.*, **35**, 809 (1902); B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(10) R. M. Ross and F. W. Raths, *ibid.*, **73**, 129 (1951).

(11) R. M. Ross, H. L. Bushey and R. J. Rolih, *ibid.*, **73**, 540 (1951); R. M. Ross, *ibid.*, **71**, 3458 (1949).

(12) *Cf.* the action of hydrogen sulfide on 2-phenyl-4-isopropylidene-5-oxazolone in the presence of triethylamine; ref. 7.

(13) The instability of the S–C bond toward alkali has been demonstrated by B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).