amount of the substituted benzoic acid, was extracted with ether. The ether solution was dried over anhydrous sodium sulfate, filtered, the ether removed and the solid residue heated to constant weight. A correction was applied for the presence of the substituted benzoic acid.

In all cases where at least one mole of sodium hydroxide was used per mole of diketone, the acids obtained accounted for at least 95% of the diketone used. In none of these cases was any diketone recovered from the ether extract.

In the case of methyl dibenzoylmethane the above procedure was modified since benzoic acid is the only acid product. The whole of the acidified solution was extracted with ether and the benzoic acid isolated as above from the ether solution.

TABLE III

Substance[a]	Wt., g.	NaOH soln., cc.	NaOH soln., %	X-$C_6H_4CO_2H$, g.	$C_6H_5CO_2H$, g.	Diketone accounted for as acids, %
I	2	35	1	..	1.02	100
II	3	50	1	0.72	0.79	95
III	3	48	1	0.70	.80	99
IV	3	50	1	1.06	.56	98
V	3	47	1	1.06	.49	98
VI	3	20	1	0.66	.31	59[c]
VI	3	40	1	1.22	.45	99
VI	3	100	1	1.22	.42	96
VI	3	40	10	1.28	.42	99
VI	3	added dropwise[b]		1.15	.45	96
VII	3	39	1	1.17	.43	98

[a] I, Methyldibenzoylmethane; II, *p*-methoxydibenzoylmethane; III, methyl *p*-methoxydibenzoylmethane; IV, *p*-chlorodibenzoylmethane; V, methyl *p*-chlorodibenzoylmethane; VI, *p*-bromodibenzoylmethane; VII, methyl *p*-bromodibenzoylmethane. [b] Thirty-seven per cent. of the diketone was recovered unchanged, thus accounting for 96% of the starting material. [c] Sixty cc. of solution containing one gram of sodium hydroxide was added over a period of five hours to the diketone refluxed with 40 cc. of distilled water.

Summary

The alkaline cleavage of three unsymmetrical diaryl beta diketones and their monomethyl derivatives is reported. The introduction of the methyl group does not affect the direction of the cleavage.

Varying amounts and concentrations of sodium hydroxide solution had little effect on the direction of cleavage of *p*-bromodibenzoylmethane.

The results support the conclusion of Bradley and Robinson that the alkaline cleavage of beta diketones is concerned with the ketonic form rather than the enolic forms.

EXETER, NEW HAMPSHIRE RECEIVED OCTOBER 3, 1945

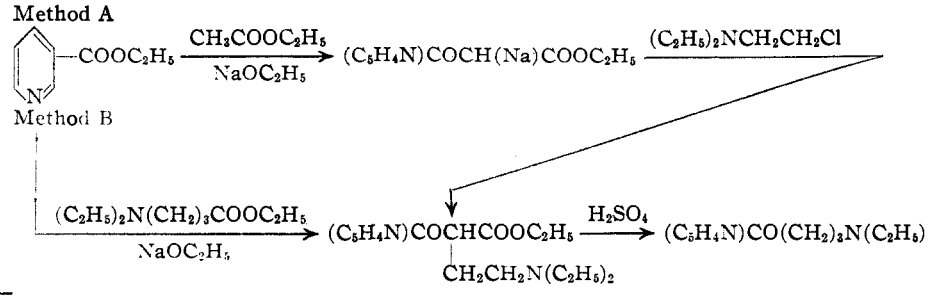
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Antimalarials. III.[1] The Synthesis of Certain Quinacrine Analogs Having N-Heterocyclic Groups in the α-Position of the Side Chain[2]

BY MELVIN S. BLOOM, DAVID S. BRESLOW AND CHARLES R. HAUSER

In continuation of our work on the preparation of quinacrine analogs having various α-substituents in the side chain,[1] we have synthesized four new diamines of the type $RCH(NH_2)CH_2CH_2CH_2N(C_2H_5)_2$ in which R is α-, β- or γ-pyridyl or 2-pyrazyl. Two of these compounds, in which R is α- and γ-pyridyl, have been coupled with 2-methoxy-6,9-dichloroacridine to form quinacrine analogs.

The diamines were prepared by the reduction of the oximes of the corresponding ketones, which were synthesized by the usual[1a] acetoacetic ester method (Method A) or, preferably, by a modification of this method (Method B). In Method A, pyridyl esters were condensed with ethyl acetate[3,4,5] and the resulting pyridoylacetic esters were alkylated with β-diethylaminoethyl chloride and cleaved. In Method B, the heterocyclic esters were condensed with ethyl γ-diethylaminobutyrate and the resulting β-keto esters were cleaved. These two methods may be illustrated by the preparation of 4-diethylamino-1-(β-pyridyl)-1-aminobutane starting from ethyl nicotinate



Method A has given only poor to fair yields of

(1) For previous papers of this series see (a) Breslow, Yost, Walker and Hauser, THIS JOURNAL, **66**, 1921 (1944); (b) Breslow, Walker, Yost and Hauser, *ibid.*, **67**, 1472 (1945).

(2) The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

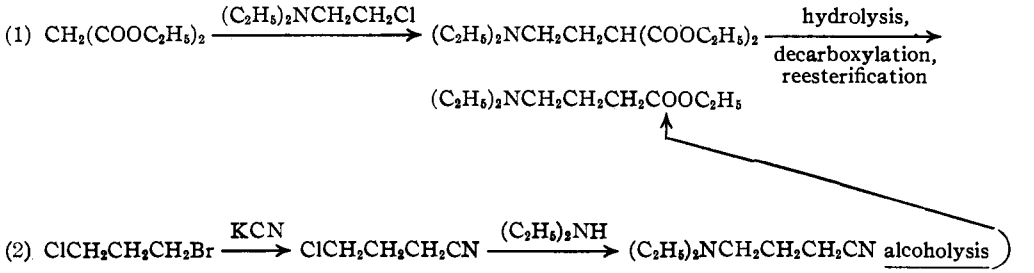
(3) Hurd and Webb, THIS JOURNAL, **49**, 546 (1927).

(4) Pinner, *Ber.*, **34**, 4234 (1901).

(5) Koelsch, *J. Org. Chem.*, **10**, 34 (1945); THIS JOURNAL, **65**, 2460 (1943).

the somewhat impure ketones. Although the condensation of the pyridyl esters with ethyl acetate gave good yields, the alkylation with β-diethylaminoethyl chloride was not very satisfactory. Apparently the heterocyclic nitrogen atom was alkylated to a considerable extent to form quaternary compounds. Pinner[4] has obtained similar results in the alkylation of α- and γ-pyridoylacetic esters with methyl, ethyl and propyl halides; in certain cases the corresponding ketones were obtained, but no yields were given.

Better results have been obtained by Method B. The ethyl γ-diethylaminobutyrate used in this method was prepared by the two following transformations; the one starting from ethyl malonate has been described by Magidson and Strukov.[6]



Although the transformation starting from trimethylene chlorobromide was carried out more conveniently, especially on a large scale, the ester obtained was always contaminated with some of the nitrile.

In Table I are given the yields of ketones, obtained from α-, β- and γ-pyridyl esters by both Methods A and B and from 2-carbomethoxypyrazine by Method B. In Table II are given the data for the oximes, obtained in excellent yields from the ketones, and for the diamines, obtained in high yields from the oximes by catalytic reduction using Raney nickel. As is frequently the case, the compounds were difficult to analyze for nitrogen.

The coupling with 2-methoxy-6,9-dichloroacridine was effected in good yields. The quinacrine analogs were obtained as trihydrochlorides which, as usual, are fine yellow powders.

Experimental[7]

Picolinic acid hydrochloride and isonicotinic acid hydrochloride were prepared by the permanganate oxidation[8] of α- and γ-picolines.[9] Nicotinic acid was obtained commercially. These acids were esterified according to the method of Camps,[10] yielding ethyl picolinate, b. p. 121° at 13 mm., ethyl nicotinate, b. p. 110° at 17 mm., and ethyl isonicotinate, b. p. 104.5° at 15 mm. The 2-carbomethoxypyrazine[11] used melted at 59°.

Pyridoylacetic Esters.—These β-keto esters, as illustrated here with ethyl β-pyridoylacetate, were prepared by a modification of the method used by Hurd and Webb[3] for the preparation of β-acetylpyridine. Alcohol-free sodium ethoxide (40 g., 0.58 mole) was added to a solution of 58.5 g. (0.38 mole) of ethyl nicotinate and 45 g. (0.51 mole) of ethyl acetate. After one hour, the reaction mixture was heated on a steam-bath for ninety minutes and then allowed to stand at room temperature for four days. Cold dilute acetic acid was added to decompose the sodium salt of the β-keto ester, and, after the addition of excess potassium carbonate, the β-keto ester was extracted with ether. The ether solution was dried over Drierite, the ether removed and the residue distilled; a 58% yield of ethyl β-pyridoylacetate was obtained, b. p. 138° at 3 mm.

In a similar manner, ethyl γ-pyridoylacetate, m. p. 54°, was obtained in 85% yield. Ethyl α-pyridoylacetate was not isolated, but was alkylated using the crude sodium salt.

Alkylation of Pyridoylacetic Esters and Cleavage. 4-Diethylamino-1-(β-pyridyl)-butanone-1.—Fine sodium wire (3.1 g., 0.13 mole) was covered with 100 ml. of dry dioxane and 25.5 g. (0.13 mole) of ethyl β-pyridoylacetate was added. After most of the sodium had reacted, the mixture was heated to 60°, a clear solution being obtained, and 20.2 g. (0.15 mole) of β-diethylaminoethyl chloride[1a] was added slowly. The reaction mixture was maintained at 50–60° for three hours, during which time a precipitate of sodium chloride formed, was allowed to stand overnight at room temperature and then refluxed for three hours. The sodium chloride was centrifuged off, the dioxane was distilled under reduced pressure and the residue was heated on a steam-bath with one liter of 10% sulfuric acid for twelve hours. The ketone was salted out with solid potassium carbonate and extracted with ether. The ether

TABLE I

$RCOCH_2CH_2CH_2N(C_2H_5)_2$[a]

R =	Method A Yield, %	B. p., °C.	Mm.	Method B Yield, %	B. p., °C.	Mm.
α-Pyridyl	21[c]	119–125.5	1.5	48[b,c]	110.5	1
β-Pyridyl	11[d]	133–136	1.5	40[b,d]	131.5–134	1.5
γ-Pyridyl	4	128	1	58[b]	122	1
2-Pyrazyl	...	.....	....	48	115–117	0.75

[a] The yields of ketones are based on the heterocyclic esters, $RCOOC_2H_5$. [b] Neutral equivalents were determined for these pyridyl ketones from samples whose boiling points are given above. Calcd. for $C_{13}H_{20}ON_2$: 220. Found: 222, 227, 226, respectively. Sharp end-points were not obtained in these titrations. Phenol red was the most satisfactory indicator. [c] Picrate, m. p. 110–111°. Calcd. for $C_{19}H_{22}O_8N_5$: N, 15.6. Found: N, 15.2. [d] Dipicrolonates, m. p. 201°, of this ketone made by both Methods A and B were prepared and showed no depression in a mixed melting point. Calcd. for $C_{33}H_{36}O_{11}N_{10}$: C, 52.9; H, 4.85; N, 18.7. Found: C, 53.0; H, 5.03; N, 18.4.

(6) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933).

(7) Microanalyses by Dr. T. S. Ma, Department of Chemistry, University of Chicago, Chicago, Illinois, and by Arlington Laboratories, Fairfax, Virginia.

(8) Singer and McElvain, "Organic Syntheses," Vol. 20, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 79.

(9) We are indebted to the Koppers Co. for a supply of α- and γ-picolines.

(10) Camps, *Arch. Pharm.*, **240**, 345 (1902).

(11) We are indebted to Dr. Charles E. Bills of Meade, Johnson and Co. for this chemical.

solution was dried over potassium carbonate, the ether removed and the residue distilled. The results are given in Table I (Method A).

Ethyl γ-Diethylaminobutyrate.—This ester was prepared by a modification of the method of Magidson and Strukov.[6] To 17 g. (0.75 mole) of fine sodium wire in 400 ml. of dry dioxane was added 120 g. (0.75 mole) of ethyl malonate. When all the sodium had reacted, β-diethylaminoethyl chloride (prepared from one mole of the hydrochloride[12]) was added with stirring at 50–60°. After stirring and heating at this temperature for three hours and allowing to stand overnight at room temperature, the reaction mixture was heated on a steam-bath for three hours. The reaction mixture was centrifuged and the dioxane distilled off up to 110°. The residue was extracted with water, the water extracted with ether and the combined solutions dried over Drierite. The ether was removed and the residue was distilled. Diethyl β-diethylaminoethylmalonate, b. p. 142–147° at 10 mm., was obtained in 61–70% yield.

This ester (118 g., 0.46 mole) was saponified with 56 g. of potassium hydroxide in 50 ml. of water by heating cautiously on a steam-bath for four hours. The reaction mixture was cooled, acidified with 140 ml. of concentrated hydrochloric acid and heated in an oil-bath at 180–190° for three hours. The water was distilled *in vacuo* and the residue dried on a steam-bath at 2 mm. The solid was extracted with 500 ml. of hot absolute ethanol, 100 ml. of concentrated sulfuric acid was added and the mixture was refluxed for four hours. The excess alcohol was distilled *in vacuo* and the residue was poured into water. The ester was salted out with potassium carbonate, extracted with ether and dried over potassium carbonate. The ether was removed and the ester distilled, b. p. 98.5–99.5° at 14 mm.; yield 68%. The over-all yield from ethyl malonate was 41–48%.

Ethyl γ-diethylaminobutyrate was also prepared by converting trimethylene chlorobromide[12] to γ-diethylaminobutyronitrile[13,14] and adding the nitrile (196 g., 1.4 moles) to 440 g. of concentrated sulfuric acid in 280 ml. of ethanol. The solution was refluxed for fourteen hours, cooled and poured into cold dilute sodium hydroxide. Solid potassium carbonate was added and the ester was extracted with chloroform. The extract was dried over potassium carbonate, the chloroform was removed and the residue was distilled. The yield of ethyl γ-diethylaminobutyrate, b. p. 96–97° at 14 mm., was 130 g. (50%), the over-all yield from trimethylene chlorobromide being 23%.

Condensation of Heterocyclic Esters with Ethyl γ-Diethylaminobutyrate and Cleavage. 4-Diethylamino-1-(β-pyridyl)-butanone-1.—To a solution of 44 g. (0.29 mole) of ethyl nicotinate dissolved in 61.5 g. (0.36 mole) of ethyl γ-diethylaminobutyrate was added 37 g. (0.54 mole) of alcohol-free sodium ethoxide in small portions. The reaction mixture was allowed to stand at room temperature for one hour, heated on a steam-bath for ninety minutes, and finally allowed to stand at room temperature for four days. The reaction mixture was dissolved in one liter of 10% sulfuric acid and decarboxylated, the ketone being isolated as described above. The results are given in Table I (Method B).

4-Diethylamino-1-(2-pyrazyl)-butanone-1 was obtained in only 5% yield using the procedure described above. Using the same procedure but employing dioxane as a solvent, the yield was increased to 48%.

Diamines and Quinacrine Analogs.—As previously described,[15] the ketones were converted to the oximes, which were reduced catalytically to the corresponding diamines (Table II).

TABLE II

R =	$RC(=NOH)CH_2CH_2CH_2N(C_2H_5)_2$ Yield, %	B. p., °C.	Mm.	$RCH(NH_2)\text{-}CH_2CH_2CH_2N(C_2H_5)_2$ Yield, %	B. p., °C.	Mm.
α-Pyridyl	88	171–174	2	78[b]	145–147	5
β-Pyridyl	80	185	1	72[c]	146–148	4
γ-Pyridyl	..[a]	.....	..	73[a,d]	162–170	5
2-Pyrazyl	87[e]	89–90 (m. p.)		75[e]	135	2

[a] The oxime was a viscous oil which decomposed on distillation. It was reduced without purification, the yield being based on the ketone. [b] *p*-Nitrobenzoate hydrochloride, m.p. 177–178°. Calcd. for $C_{20}H_{26}O_3N_4 \cdot 2HCl \cdot 2H_2O$: N, 11.7. Cl^-, 14.8. Found: N, 11.6. Cl^-, 14.8. [c] Picrate, m. p. 198–199°. Calcd. for $C_{19}H_{26}O_7N_6$: N, 18.7. Found: N, 18.3. [d] *p*-Nitrobenzoate, m. p. 144.5–145°. Calcd. for $C_{20}H_{26}O_3N_4$: N, 15.1. Found: N, 14.7. [e] The oxime was analyzed. Calcd. for $C_{12}H_{20}ON_4$: N, 23.7. Found: N, 23.1.

The α- and γ-pyridyldiamines were coupled with 2-methoxy-6,9-dichloroacridine, the free bases being purified and converted into hydrochlorides as described previously.[15]

The α-pyridyl analog, after recrystallization from a mixture of acetone and alcohol, melted at 181–185°.

Anal.[15] Calcd. for $C_{27}H_{31}ON_4Cl \cdot 3HCl \cdot 2H_2O$: Cl^-, 17.49. Found: Cl^-, 17.41.

The γ-pyridyl analog, after recrystallization from a mixture of alcohol and isopropyl ether, melted at 212–214°.

Anal.[15] Calcd. for $C_{27}H_{31}ON_4Cl \cdot 3HCl \cdot H_2O$: Cl^-, 18.02. Found: Cl^-, 18.06.

Summary

The synthesis of four 4-diethylamino-1-N-heterocyclo-1-amino-butanes is described, the heterocyclic rings being α-, β- and γ-pyridyl and 2-pyrazyl.

Two of these, the α- and γ-pyridyl compounds, have been converted into quinacrine analogs.

DURHAM, N. C. RECEIVED AUGUST 9, 1945

(12) We are indebted to the Dow Chemical Co. for a supply of this chemical.

(13) Allen "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 156.

(14) Utermohlen and Hamilton, THIS JOURNAL, **63**, 156 (1941).

(15) Macroanalyses by Miss Mary K. Scholl of this Laboratory.