immediately placed in an ice bath and cooled until the acetic acid commenced to crystallize. The cooling bath was then removed and the solution stirred (magnetically) for 9 hr. at room temperature, heated to reflux and left at room temperature overnight. The silver bromide was separated by filtration of the cooled solution and the filtrate was distilled under reduced pressure. After distillation of the acetic acid there was obtained 31.5 g. (90.5%) of 2-(α-acetoxyethyl)pyridine, b.p. 112–113° (12 mm.), [reported[4] b.p. 109–111° (16 mm.)].[14]

The infrared spectrum (pure liquid) of the acetate prepared by this route was identical with the infrared spectrum of the acetate prepared by rearrangement of 2-ethylpyridine oxide (IV).

2-(α-Hydroxyethyl)pyridine (V). To 9.0 g. (0.225 mole) of sodium hydroxide, 83 ml. of water and 57 ml. of methanol under a nitrogen atmosphere was added 31.5 g. (0.191 mole) of 2-(α-acetoxyethyl)pyridine. The solution was heated under reflux for 11.5 hr., transferred to a continuous extractor, diluted with 300 ml. of saturated sodium chloride solution and continuously extracted with benzene for 25 hr. Distillation of the extract yielded 21.37 g. (91%) of 2-(α-hydroxyethyl)pyridine, b.p. 93.5–94.0° (7 mm.) n_D^{25} 1.5223 (reported[5] b.p. 85–89° (5 mm.) n_D^{25} 1.5253).[15] The picrolonate, recrystallized from ethanol, melted at 184–186° dec.[15]

2-Pyridyl methyl ketone (VI). To a solution of 105 g. of *N*-bromosuccinimide, 1200 ml. of acetone, and 120 ml. of water was added 31.64 g. (0.257 mole) of 2-(α-hydroxyethyl)-pyridine and 2 ml. of glacial acetic acid. The pale yellow solution turned red within 12 hr. and pale yellow again after a total of 20.5 hr.[16] The reaction mixture was allowed to stand for a total of 48 hr. before being neutralized with solid sodium carbonate. A sodium thiosulfate solution was added to the lacrimatory mixture until a drop of the mixture failed to produce a blue color when placed on a piece of acidified starch iodide paper. The lacrimatory properties of the two phase system disappeared at this time. The cooled solution was filtered and the filtrate made acidic with hydrochloric acid (*p*H 1). After removal of the acetone by distillation, the residue was made basic (*p*H 9) and the aqueous solution distilled. The 1.0 l. of distillate was continuously extracted with benzene for 36 hr. Distillation of the extract yielded 20.00 g. (65%) of 2-pyridyl methyl ketone, b.p. 82–83.5° (13–15 mm.) n_D^{25} 1.5153 [reported[17] b.p. 78° (12 mm.)].

The phenylhydrazone recrystallized from methanol-water melted at 156–158° (reported[17] m.p. 155.5–156°).

2-Pyridyl isopropyl ketone[18] (VII). To a solution prepared from 4.5 g. (0.116 mole) of potassium and 230 ml. of *t*-butyl alcohol (distilled from 3 g. of sodium), 300 ml. of sodium-dried benzene was added. To the stirred refluxing solution under a nitrogen atmosphere was added, as fast as possible, 7.0 g. (0.058 mole) of 2-pyridyl methyl ketone. This addition was followed immediately by the addition, during 1 min., of 24.6 g. (0.174 mole) of methyl iodide in 5 ml. of dry benzene. The solution was maintained at reflux for an additional 4 min., then quenched with 50 ml. of ice water. After the addition of 25 ml. of concd. hydrochloric acid, the solution was concentrated under reduced pressure. The residue was made basic by the addition of 20 g. of potassium hydroxide (*p*H 11). After saturating the solution with solid sodium chloride, it was extracted with eight portions of ether. The combined ether solutions were filtered through and dried over sodium sulfate, concentrated under reduced pressure, and distilled. There was obtained a forerun of 1.37 g., b.p. 73.5–87.5° (7 mm.) n_D^{25} 1.5084–1.5053, followed by 4.15 g. (48%) of 2-pyridyl isopropyl ketone, b.p. 87.5–88.5° (7 mm.) n_D^{25} 1.5000–1.4989 (reported[19] 107–108° (25 mm.) n_D^{25} 1.5028). The pot residue amounted to 1.0 g.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H 7.43. Found: C, 72.56; H 7.69.

The 2,4-dinitrophenylhydrazone after one recrystallization from ethyl acetate melted at 180.0–181.6°. The analytical sample melted at 181.0–181.4° (reported[19] m.p. 181.0–181.5°).

Anal. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.61; H, 4.59. Found: C, 54.46; H, 4.70.

When equimolar quantities of potassium, methyl iodide, and methyl 2-pyridyl ketone were used, the same product was obtained in 15% yield. The infrared spectrum was identical with that of the ketone prepared above, and a mixture melting point of the 2,4-dinitrophenylhydrazones was undepressed.

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(14) We have repeated the preparation of 2-(α-acetoxyethyl)pyridine using the procedure of Boekelheide and Linn[4] and obtained a 67% yield of the acetate. b.p. 105–110° (9–10 mm.) n_D^{25} 1.4893– 1.4923 (reported[5] n_D^{25} 1.4913).

(15) Hydrolysis of the acetate produced *via* the *N*-oxide route[4] yielded the alcohol in 75% yield, b.p. 93.5–94.5° (7 mm.) n_D^{25} 1.5220–1.5230.

Anal. Calcd. for C_7H_9ON: C, 68.27; H, 7.37. Found: C, 68.49; H, 7.65.

The ultraviolet absorption spectrum in ethanol showed: $\lambda_{max.}$ 256 mμ log ε 3.48, $\lambda_{max.}$ 261 mμ log ε 3.55, $\lambda_{max.}$ 267.5 mμ log ε 3.23.

The picrolonate prepared from this material was recrystallized from ethanol and melted at 183.0–185.6° dec.

Anal. Calcd. for $C_{17}H_{17}N_5O_6$: C, 52.71; H, 4.42. Found: C, 52.93; H, 4.79.

(16) B. C. Anderson, Ph.D. thesis, Massachusetts Institute of Technology, 1955.

(17) P. C. Teague, A. R. Ballentine, and G. L. Rushton, *J. Am. Chem. Soc.*, **75**, 3429 (1953).

(18) S. Bertucat, *Compt. Rend.*, **232**, 1758 (1951), has claimed the synthesis of this compound and three of its derivatives; however, no physical properties were reported for the compound and we have been unable to prepare any of the recorded derivatives.

(19) H. R. Henze and M. B. Knowles, *J. Org. Chem.*, **19**, 1127 (1954).

Cyclizations Leading to 2-Acylpyrroles and 2-Pyrrolecarboxylic Esters[1,2]

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Prior to the outset of this investigation, the reductive condensation of certain β-diketones and β-ketoaldehydes with ethyl α-oximinoacetoacetate[3–5]

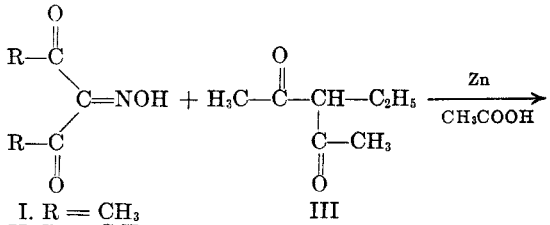
(1) Studies in the Pyrrole Series, XXIX. Paper XXVIII, B. Harrell and A. H. Corwin, *J. Am. Chem. Soc.*, **78**, 3135 (1956).

(2) This work was supported by a research grant (NSF-G 1195) from the National Science Foundation.

(3) H. Fischer and E. Fink, *Z. physiol. Chem.*, **280**, 123 (1944).

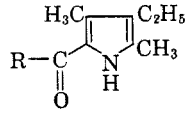
and diethyl oximinomalonate[6] on the one hand and with ethyl oximinocyanoacetate[6] on the other had been shown to give 2-pyrrolecarboxylic esters[3-6] and 2-pyrrolecarbonitriles,[6] respectively. More recently two further publications[7,8] have described additional condensations of this same general type which lead to other 2-pyrrolecarboxylic esters[7,8] and even to tetraalkylpyrroles.[8] In every case cyclization is accompanied by the loss of an acyl or an alkoxycarbonyl group which was initially present in the oximino moiety.

In order to determine whether an adaptation of this cyclization reaction might constitute a useful synthetic route to 2-acylpyrroles,[9] the reductive condensation of each of two α-oximino-β-diketones with 3-ethyl-2,4-pentanedione (III) was investigated. The reaction of 3-oximino-2,4-pentanedione (I) with III in the presence of zinc dust and acetic acid provided 2-acetyl-4-ethyl-3,5-dimethylpyrrole (IV) in 16% yield. Under similar conditions 2-oximino-1,3-diphenyl-1,3-propanedione (II) and III afforded an 11% yield of 2-benzoyl-4-ethyl-3,5-dimethylpyrrole (V). Pyrroles IV and V had been previously prepared by other investigators *via* the acylation[10,11] of 3-ethyl-2,4-dimethylpyrrole. This appears to be the first reported instance in which an α-oximino-β-diketone has participated in a pyrrole ring synthesis involving scission of one of its acyl groups. The presence of the 3-ethyl group in III apparently precludes the usual Knorr condensation. It has long been known that an aminomethyl monoketone may occasionally take part in a similar cyclization[12,13] so that a 2-acylpyrrole



I. R = CH_3
II. R = C_6H_5

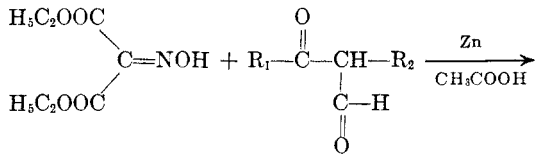
III



IV. R = CH_3
V. R = C_6H_5

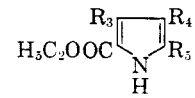
by-product sometimes accompanies the expected product of a Knorr condensation.

In connection with a synthetic program in progress in this laboratory, it was desirable to develop a convenient synthesis for ethyl 3-ethyl-4-methyl-2-pyrrolecarboxylate (X). Our previous synthesis[6] of ethyl 3,4-dimethyl-2-pyrrolecarboxylate (IX) from 2-methyl-3-oxobutyraldehyde (VII) and diethyl oximinomalonate (VI) led us to attempt the synthesis of X *via* reductive condensation of VI with 2-methyl-3-oxovaleraldehyde (VIII). Surprisingly, condensation proceeded in the opposite sense to provide ethyl 5-ethyl-4-methyl-2-pyrrolecarboxylate (XI), an isomer of X, in a yield of only 2%. As the reported melting points of pyrrolecarboxylic esters X[11,14] and XI[4] lie within 4° of one another, unequivocal identification of the product was achieved through conversion to the corresponding dipyrrylmethane (XII)[4] in 65% yield. The isolation of XI from this cyclization reaction

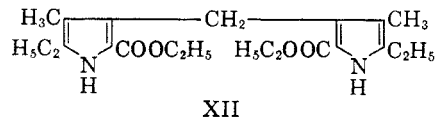


VI

VII. $R_1 = R_2 = CH_3$
VIII. $R_1 = C_2H_5$, $R_2 = CH_3$



IX. $R_3 = R_4 = CH_3$, $R_5 = H$
X. $R_3 = C_2H_5$, $R_4 = CH_3$, $R_5 = H$
XI. $R_3 = H$, $R_4 = CH_3$, $R_5 = C_2H_5$

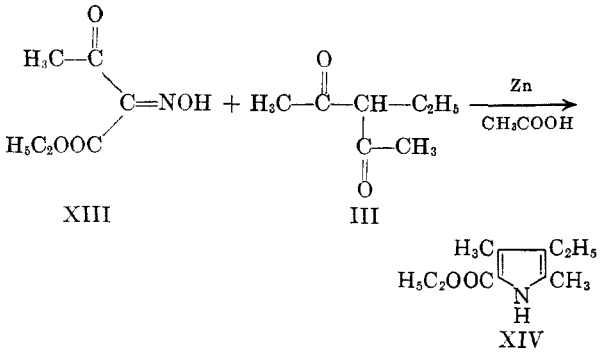


XII

parallels the experience of Fischer and Fink,[4] who obtained XI and ethyl 4,5-dimethyl-2-pyrrolecarboxylate from the reductive condensation of ethyl α-oximinoacetoacetate with VIII and VII, respectively.

In an earlier communication[6] we reported the synthesis of ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (XIV) in 65% yield from the reaction of diethyl oximinomalonate (VI) with 3-ethyl-2,4-pentanedione (III) in the presence of zinc and acetic acid. In the course of this work the analogous reductive condensation of ethyl α-oximinoacetoacetate (XIII) and III was carried out to give this same pyrrole (XIV) in 47% yield. A number of very closely related pyrrole syntheses from α-oximinoacetoacetic esters and 3-substituted 2,4-pentanediones have been reported recently.[7,8]

(4) H. Fischer and E. Fink, *Z. physiol. Chem.*, **283**, 152 (1948).
(5) G. H. Cookson, *J. Chem. Soc.*, 2789 (1953).
(6) G. G. Kleinspehn, *J. Am. Chem. Soc.*, **77**, 1546 (1955).
(7) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).
(8) A. W. Johnson, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 4254 (1958).
(9) H. Fischer and E. Fink attempted such a synthesis of 2-acylpyrroles by reductive condensation of 3-oximino-2,4-pentanedione with each of two β-ketoaldehydes. In neither case was a pyrrole product isolated. See reference 4.
(10) H. Fischer and P. Viaud, *Ber.*, **64B**, 193 (1931).
(11) W. Siedel, *Z. physiol. Chem.*, **231**, 167 (1935).
(12) H. Fischer, H. Beyer, and E. Zaucker, *Ann.*, **486**, 55 (1931).
(13) G. K. Almström, *Ann.*, **409**, 291 (1915).
(14) H. Fischer, W. Siedel, and L. le T. d'Ennequin, *Ann.*, **500**, 190 (1933).



XIII III XIV

EXPERIMENTAL[15]

2-Acetyl-4-ethyl-3,5-dimethylpyrrole (IV). The reductive condensation of 50 mmol. of 3-oximino-2,4-pentanedione[16,17] with 50 mmol. of 3-ethyl-2,4-pentanedione[18,19] was carried out in the presence of zinc dust, sodium acetate, and aqueous acetic acid using the procedure[6] described for the preparation of 2-carbethoxy-3,5-dimethylpyrrole from diethyl oximinomalonate and 2,4-pentanedione. Yield of crude product, 1.3 g. or 16%. A product melting at 112–114.5° was obtained after a single recrystallization from methanol. Additional recrystallization from aqueous methanol and from isoöctane afforded an analytically pure sample of m.p. 114.5–115.5°; lit.,[10,11] m.p. 114–115°, 111–112°.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.36; H, 9.09.

2-Benzoyl-4-ethyl-3,5-dimethylpyrrole (V). The procedure was essentially that employed for the preparation of IV with a few minor modifications. In this instance 25 mmol. each of 3-ethyl-2,4-pentanedione[18,19] and of 2-oximino-1,3-diphenyl-1,3-propanedione[20] were employed. Zinc dust was removed from the brown viscous, semisolid product by filtration of its solution in hot benzene-methanol. Evaporation of the filtrate to a sirupy, semicrystalline residue and trituration of this residue with a little ether produced a viscous slurry of the crystalline product, which was collected on the filter. Yield of crude product, 0.6 g. or 11%; m.p. 132–139°. Recrystallization from aqueous methanol gave a purer product of m.p. 140.5–141.5°; lit.,[11] m.p. 143°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.13; H, 7.63.

Isolation and identification of ethyl 5-ethyl-4-methyl-2-pyrrolecarboxylate (XI) *from the reductive condensation of diethyl oximinomalonate* (VI) *with 2-methyl-3-oxovaleraldehyde* (VIII). To 30 ml. of glacial acetic acid previously heated to 85° was added with stirring 1) 7.9 g. of anhydrous sodium acetate, 2) a solution of 7.7 g. (57 mmol.) of the sodium salt of 2-methyl-3-oxovaleraldehyde in 10 ml. of water and 5 ml. of acetic acid, and 3) a solution of 9.5 g. (50 mmol.) of diethyl oximinomalonate in 7 ml. of acetic acid. Addition of 11 g. of zinc dust was then begun at such a rate that the temperature rose to and remained in the range 100–106°. When all of the zinc dust had been introduced with vigorous stirring, the reaction mixture was heated 15 min. longer, then poured into 150 ml. of ice water. An oil containing some solid separated upon refrigeration. This was extracted with ether, and the residue remaining after evaporation of the ether was distilled under reduced pressure in order to separate the pyrrole from less volatile materials. A broad fraction of b.p. 80–155° at 16–20 mm. was collected, treated with aqueous sodium hydroxide, then extracted with ether. Recrystallization from ethanol of the oily crystalline solid obtained upon evaporation of this ether extract gave 170 mg. or 2% yield of pyrrole XI, m.p. 72–77°; lit.,[3] m.p. 79°.

Since the isomeric ethyl 3-ethyl-4-methyl-2-pyrrolecarboxylate (X)[11,14] is reported to melt at 75° or 76°, the identification of our pyrrolecarboxylic ester product of m.p. 72–77° was achieved through conversion to diethyl 3,3′-methylenebis(5-ethyl-4-methyl-2-pyrrolecarboxylate) (XII). Crude XII was obtained in 65% yield by heating our product with formaldehyde in aqueous ethanol in the presence of a small amount of concd. hydrochloric acid. Recrystallization from ethanol afforded a pure product of m.p. 193–196°; lit.,[4] m.p. 190°. The isomeric diethyl 5,5′-methylenebis(3-ethyl-4-methyl-2-pyrrolecarboxylate)[21] is reported to melt at 148°.

Anal. Calcd. for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07. Found: C, 67.28; H, 8.30.

Ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (XIV). The preparative procedure was the same as that employed in the preparation of IV except that the zinc dust rather than the oximino compound was added gradually to the other reactants. Condensation of 30 mmol. each of ethyl α-oximinoacetoacetate and of 3-ethyl-2,4-pentanedione in this manner gave 2.75 g. or 47% yield of product of m.p. 89–90°; lit.,[6] m.p. 90–91°.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.46; H, 8.94.

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(15) All melting points were determined on the Fisher-Johns melting point apparatus.

(16) L. Wolff, P. Bock, G. Lorentz, and P. Trappe, *Ann.*, **325**, 139 (1902).

(17) The authors wish to thank Mr. Peter M. Eller for the preparation of this intermediate.

(18) N. P. Buu-Hoï and D. Guettier, *Rec. trav. chim.*, **65**, 505 (1946).

(19) The authors wish to thank Mr. Wilford L. Mendelson for the preparation of this intermediate.

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Substituted Aminobenzoquinolines

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This communication deals with the preparation of a number of substituted 1-amino-3-methylbenzo[*f*]quinolines and 4-amino-2-methylbenzo[*h*]quinolines for trials against *E. histolytica*.

The compounds were prepared by the action of 1-chloro-3-methylbenzo[*f*]quinoline or 4-chloro-2-methylbenzo[*h*]quinoline on the appropriate amine in boiling ethanol (Method I). Benzylamine, 2-phenylethylamine, 4-phenoxybutylamine, and 3-diethylaminopropylamine did not react under these conditions; in these cases, the reaction was carried out by heating the reactants in phenol (Method II) and the products isolated as the salicylate.

The condensation of 1-naphthylamine and ethyl acetoacetate in the presence of iodine and subsequent cyclization of the resulting anil in hot liquid paraffin yielded 4-hydroxy-2-methylbenzo[*h*]quinoline which on treatment with phosphorus oxychloride gave the intermediate 4-chloro-2-methylbenzo[*h*]quinoline; a similar procedure with 2-naphthylamine yielded 1-chloro-3-methylbenzo[*f*]quinoline.[1]

(1) A. Albert, D. J. Brown, and H. Duewell, *J. Chem. Soc.*, 1284 (1948).