Tetrahedron Letters, Vol. 33, No. 38, pp. 5577-5580, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

SYNTHESIS OF PYRIDO[2,3,4-kl]ACRIDINES
A BUILDING BLOCK FOR THE SYNTHESIS OF PYRIDOACRIDINE ALKALOIDS

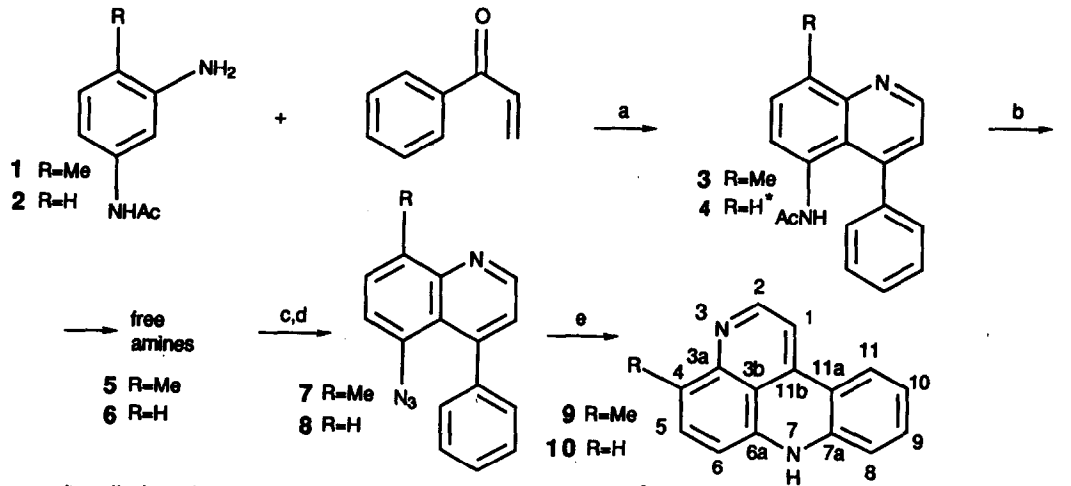
Gari Gellerman, Amira Rudi and Yoel Kashman*

School of Chemistry, Tel Aviv University, Tel Aviv 69978, Israel

Abstract: Two new syntheses have been developed for the preparation of substituted pyrido[2,3,4-kl]acridines. The first synthesis involves a Skraup reaction and a nitrene insertion whereas the second includes a new pyridine ring synthesis starting from a 1-amino group on acridine and taking advantage of the active 9-position of the latter heterocycle.

The number of fused ring alkaloids having the pyrido[2,3,4-kl]acridine skeleton has increased rapidly in the last several years[1]. Their biological activity[1] and the novel ring system render them particularly appealing both as targets for synthesis and as candidates for pharmacological evaluation. Of special interest was to develop a synthesis which will afford the naked pyridoacridine skeleton as a substrate for the study of electrophilic substitutions of this heterocycle and at the same time also enable the synthesis of a variety of substituted pyridoacridines. Two new syntheses, described below, have been developed for these purposes. These syntheses enable the preparation of the unsubstituted pyridoacridine and several of its derivatives which may also be used to generate building blocks for more complex alkaloids of this group.

The first synthesis started from 2-amino-4-acetamidotoluene (**1**) or 3-aminoacetanilide (**2**) which reacted with vinylphenylketone under the Skraup reaction conditions[2] to afford the corresponding 4-phenylquinolines **3** and **4** respectively[3]. Characteristic in the ^{1}H NMR spectra of compounds **3** and **4** are the H-2 and H-3 signals, at δ8.86d and 7.16d (J=4.2 Hz) for **3**, and δ8.85d and 7.19d (J=4.2 Hz) for **4**, and the high-field shift of the N-acetyl (δ1.45s and 1.42s for **3** and **4**, respectively) due to the diamagnetic effect of the neighbour phenyl group in the *peri* position. Acid hydrolysis of the acetamide groups of **3** and **4**, to yield the amines **5** and **6** respectively, followed by diazotization and reacting of the obtained diazonium salt with an azide ion resulted in compounds **7** and **8**[5]. Each one of the latter compounds afforded, *via* a nitrene intermediate[6], by heating to 200°C in durene, the desired pyridoacridine system, compounds **9** and **10** respectively[7]. Characteristic, *inter alia*, for the pyridoacridines (compounds **9**, **10**, **14** and **15** but not **12**, *vide infra*) is the red color that develops in acidic media[8] and the coupling constants of 4.8 Hz for H-1 and H-2, in the ^{1}H-NMR spectrum, in comparison to 4.2-4.4 Hz for H-2 and H-3 in compounds **3-8**, before closing the fourth, pyridine, ring. Pyridoacridine alkaloids have, indeed, already been synthesized using other methods[9]; however these methods seem to be less suitable, in comparison to the two ways described in this report, for the preparation of a variety of substituted pyridoacridines.

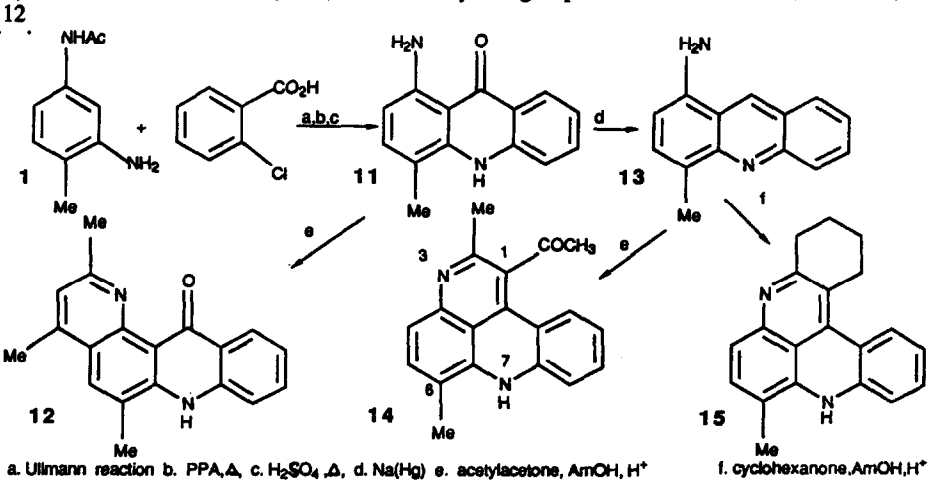


a. m-nitrosulfonic acid sodium salt ,HOAc, , b.H_2SO_4, , c.$NaNO_2$, H^+, 0^0c, d. NaN_3, e. 200°c

* 4 is accompanied by the second possible isomer in a ratio of 1:4

A second approach towards the synthesis of the pyridoacridines started from acridone **11**. Compound **11** was prepared in two steps from compound **1** and o-chlorobenzoic acid, that is, *via* a Ullmann reaction to afford a substituted diphenylamine, followed by acid catalyzed cyclization of the pyridine ring of **11** (polyphosphoric acid, 125°C, 1 hour). From compound **11** we tried to form the second pyridine ring of the pyrido[2,3,4-kl]acridine by a Friedländer quinoline synthesis[10]. In this synthesis o-aminobenzophenones react with active α-methylene carbonyl compounds to form quinolines. Indeed, we were aware of the fact that the carbonyl in 9-acridone, because of conjugation with the NH group, is not a regular carbonyl group. Nevertheless, we have reacted compound **11** with acetylacetone. The reaction left the CO-group intact, however it formed a quinoline system fused with the aniline ring of **11**, by an attack ortho- to the amine position, to give compound **12**[11]. The pyrido[2,3-a]acridine structure of **12** was unequivocally established from its NMR data[11], characteristic were the three methyls, two aromatic singlets and the four protons of the o-disubstituted aromatic ring.

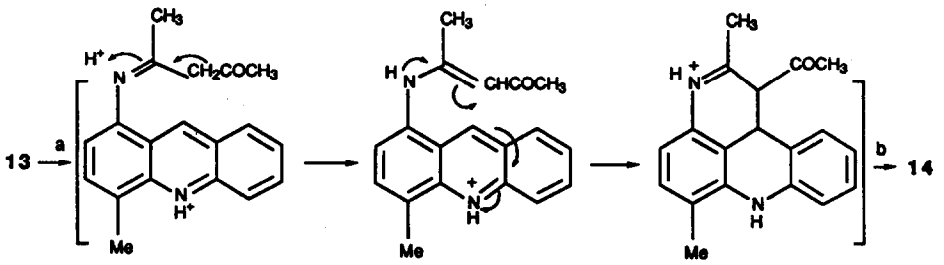
In a different approach we tried to take advantage of the known reactions of the active 9 position in acridines, under neutral conditions, with active methylene groups as in $NCCH_2CO_2Et$, CH_3NO_2, $CH_2(CN)_2$ etc.[12].



a. Ullmann reaction b. PPA,Δ, c. H_2SO_4,Δ, d. Na(Hg) e. acetylacetone, AmOH, H^+ f. cyclohexanone,AmOH,H^+

For this purpose compound **11** was reduced with Na(Hg) to 1-amino-4-methylacridine (**13**) . Heating compound **13** with eg. $NCCH_2CO_2Et$ left compound **13** intact. However, when catalytic amounts of acid were added to the reaction mixture of **13** with acetylacetone a reaction took place. A pure adduct (**14**) could have been isolated upon chromatography[14]. The structure of compound **14**, $C_{19}H_{16}N_2O$ (eims, m/z 288, 100%) 1-acetyl-2,6-dimethylpyrido[2,3,4-kl]acridine, was elucidated mainly from its NMR data[14] (comparison of the chemical shifts with those of other pyridoacridines[7,1], d-NOE, COSY and CH-correlation experiments).

We assume that at the first stage of the synthesis the 1-amino group forms a Schiff base with one of the two carbonyl groups of acetylacetone (in the absence of a carbonyl, eg. with $NCCH_2CO_2Et$, there is no reaction). In the second step the methylene in the α position to the original carbonyl, and now α to the imine reacts with the pyridine ring of the acridine in a 1,4-intramolecular addition followed by oxidative aromatization by air in the following possible mechanism:



a. acetylacetone , AmOH, H^+, Δ b. air oxidation

The easiness by which the second intramolecular cyclization step takes place could be demonstrated by the reaction of cyclohexanone with compound **13**. In this case after the initial Schiff base formation the less reactive α-methylene, of cyclohexanone reacts with the pyridine ring of the acridine to yield compound **15**[15] although it is only activated by the vicinal imine.

The above described two new synthesis are expected to be useful for the preparation of a variety of pyrido[2,3,4-kl]acridine derivatives including adequate building blocks for pyridoacridine alkaloids by starting from suitable substituted benzenes as starting materials.

References and Notes

1. (a) Schmitz, F.J.; Agarwal, S.K.; Gunasekera, S.P.; Schmidt, P.G.; Shoolery, J.N., J. Am. Chem. Soc. 1983, 105, 4835; (b) Gunawardana, G.P.; Kohmoto, S.; Gunasekara, S.P.; McConnell, O.; Kohen, F.E., J. Am. Chem. Soc. 1988, 110, 4856; (c) Charyulu, G.A.; McKee, T.C.; Ireland, C.M., Tet. Letters, 1989, 30, 4201; (d) Cooray, N.M.; Scheuer, P.J.; Parkanyi, L.; Clardy, J., J. Org. Chem. 1988, 53, 4619; (e) Molinski, T.F.; Ireland, C.M., J. Org. Chem. 1989, 54, 4256; (f) Carroll, A.R.; Scheuer, P.J., J. Org. Chem. 1990, 55, 4427; (g) Rudi, A.; Kashman, Y., J. Org. Chem. 1989, 54, 5331; (h) He Hay-yin; Faulkner, D.J., J. Org. Chem. 1991, 56, 5369.
2. Lown, J.W. and Sim Soo-Khoon, Can. J. Chem. 1976, 54, 2563.
3. Compounds **3** and **4** were prepared according to the synthesis of o-nitro phenyl quinolines[2]. Compound **3**, mp 214°C (acetone), $C_{18}H_{16}N_2O$ (m/z 276), δ_H ($CDCl_3$): 8.86d (J=4.2 Hz), 7.72d (J=7.7),7.53d (J=7.7), 7.48m, 7.32m (5H), 7.16d (J=4.2), 6.84 brs (NH), 2.81s (Me), 1.45s (NCO CH_3). Compound **4**, amorphous powder, $C_{17}H_{14}N_2O$ (m/z 262), δ_H 8.85d (J=4.2 Hz), 7.96d (J=8.0), 7.70d (J=8.0),7.40m (6H), 7.19d (J=4.2), 1.42s (NCO CH_3).

4. Acid hydrolysis of compound **3** and **4** (80% H_2SO_4, 130°C 2 hours) afforded after the regular work-up compounds **5** and **6** respectively, in a yield of 70%. Compound **5**, a yellow oil, $C_{16}H_{14}N_2$ (m/z 234), δ_H ($CDCl_3$) 8.74d (J=4.3 Hz), 7.27m (6H), 6.96d (J=4.3), 6.47d (J=7.6), 2.62s (Me). Compound **6**, a yellow oil, $C_{15}H_{12}N_2$ (m/z 220), δ_H ($CDCl_3$) 8.78d (J=4.3 Hz), 7.59t (J=8.2), 7.40m (6H), 7.02d (J=4.3), 6.63d (J=8.2).

5. Compound **5** or **6** was dissolved in 15% HCl and cooled down to 0°C, then $NaNO_2$ followed by NaN_3 were added. The usual work-up gave a dark red oil in 75% yield, compound **7** or **8** respectively. Compound **7**, $C_{16}H_{12}N_4$ (m/z 232, M-N_2), ν_{max} 2110 cm^{-1}, δ_H ($CDCl_3$) 8.91d (J=4.4 Hz), 7.60d (J=7.8), 7.17m (7H),2.82s (Me); Compound **8**, $C_{15}H_{10}N_4$ (m/z 218, M-N_2), ν_{max} 2112 cm^{-1}, δ_H ($CDCl_3$) 8.89d (J=4.2 Hz), 7.99d (J=8.2), 7.71t (J=8.2), 7.40m (3H), 7.30m (3H), 7.21d (J=4.2).

6. Cadogen, J.I.G.; Synthesis 1969, 11.

7. Compound **7** or **8**, dissolved in durene under argone was heated for 30 minutes at 200°C. Compound **9** or **10**, respectively, were obtained following work-up in 50% yield; Compound **9**, amorphous powder mp > 300°C, $C_{16}H_{12}N_2$ (msci, m/z 233, MH^+), ν_{max} 3250, 1615, 1520, 1220, 1080, 870 cm^{-1}, δ_H (d_6-DMSO)10.40 brs (NH) 8.55d (J=4.8 Hz, H-2), 7.97d (J=8.0, H-11), 7.42d (J=4.8, H-1), 7.35t (J=8.0, H-9), 7.34d (J=8.0, H-5), 6.98d (J=8.0, H-8), 6.95t (J=8.0, H-10), 6.82d (J=8.0, H-6), δ_C 150.2d (C-2), 147.0s (C-3a), 140.4s (C-11b), 139.9s (C-7a), 136.6s (C-6a), 132.0d (C-9), 131.1d (C-5), 124.2d (C-11), 121.3s (C-4), 120.4d (C-10), 118.2s (C-3b), 115.9s (C-11a), 115.6d (C-8), 106.2d (C-1), 102.7d (C-6), 13.7q (Me). Compound **10**, amorphous powder mp > 300°C, $C_{15}H_{10}N_2$ (m/z 218), δ_H (d_6-DMSO) 10.48 brs(NH) 8.46d (J=4.8 Hz, H-2), 8.08d (J=8.0, H-11), 7.58t (J=8.0, H-5), 7.49t (J=8.0, H-9), 7.48d (J=4.8, H-1), 7.17d (J=8.0, H-8), 7.13d (J=8.0, H-4), 7.06t (J=8.0, H-10, 6.82d (J=8.0, H-6).

8. Compound **9** λ_{max} (MeOH) 466 (3500), 372 (2500), 322 (7600), 264 (13700), 234 (13100); λ_{max} (MeOH, H^+) 518 (4300), 368 (2700), 288 (13500), 240 (12400), 222 (11300); Compound **10** λ_{max} (MeOH) 452 (1700), 368 (1100), 320 (3150), 266 (6700), 220 (13400); λ_{max} (MeOH, H^+) 526 (1800), 504 (1980), 284 (9100), 234 (8600), 214 (9800).

9a. Stille, J.K.; Echavarren, A.M., J. Am. Chem. Soc. 1988, 110, 4051; (b) Gomez-Bergoa, E.; Echavarren, A.M., J. Org. Chem. 1991, 56, 3497; (c) Ciufolini, M.A.; Byrne, N.E., J. Am. Chem. Soc. 1991, 113, 8016; (d) Prager, R.H.; Tsopelas, C.; Heisler, T. Aust. J. Chem. 1991, 44, 277; (e) Weiss, R.; Katz. J.L.; Sitzungsber. Akad. Wiss. Wien, IIb, 1928, 137, 701.

10. Friedländer, P., Ber. 1882, 15, 2572; Cheng Chia-Chung, Yan Shou-Jen; Org. Reactions, John Wiley & Sons, N.Y. 1982 Vol. 28, chap. 2, p. 37.

11. Warming of compound **11** (prepared according to Goldberg, A.R.; Kelly, W., J. Chem. Soc. 1946, 102) with acetylacetone in amylalcohol with traces of H_2SO_4 at 130° for 1.5 hours afforded after work-up compound **12** in 40% yield: amorphous powder, $C_{19}H_{16}N_2O$ (m/z 288); δ_H ($CDCl_3$; d_4-MeOH 95:5) 8.53d (J=8.0 Hz), 8.26d (J=8.0), 7.84t (J=8.0), 7.83s, 7.54t (J=8.0), 7.22s, 2.87s, 2.80s, 2.74 (3 x Me's).

12. Kröhnke, F.; Honig, H.L., Liebigs Ann. Chem. 1959, 624, 97.

13. Compound **13** was prepared from compound **11** according to Koft, E.; Case, F.H., J. Org. Chem., 1962, 27, 865; oil, $C_{14}H_{12}N_2$ (m/z 208); δ_H ($CDCl_3$), 8.775s, 8.258d (J=8.8 Hz), 7.991d (J=8.4), 7.764dt (J=1.3,8), 7.517t (J=7.7), 7.425d (J=7.2), 6.708d (J=7.2) 2.82s (Me).

14. Compound **13** afforded compound **14**, under the same conditions as for the preparation of **12**, orange oil, $C_{19}H_{16}N_2O$ (m/z 288), ν_{max} 1682 cm^{-1}; δ_H ($CDCl_3$) 7.59 brs (NH), 7.52dd (J=8.2, 1.2 Hz, H-11), 7.36bd (J=8.0, H-5), 7.30ddd (J=8.4, 7.1, 1.2, H-9), 7.28d (J=8.0, H-4), 7.01dd (J=8.4, 1.2, H-8), 6.89ddd (J=8.2, 7.1, 1.2, H-10), 2.53s (Me on C-2), 2.48s ($COCH_3$), 2.26s (Me on C-6); δ_C 208.7s (CO), 154.3s (C-2), 147.3s (C-3a), 140.5s (C-11b), 135.8s (C-7a), 134.2s (C-6a), 133.2d (C-5), 131.6d (C-9), 127.7d (C-11), 124.1s (C-1), 121.2d (C-10), 116.3s (C-3b) 116.2d (C-8), 116.0s (C-11a) 115.8d (C-4), 110.8s (C-6), 95.7s (C-3b), 32.4q ($COCH_3$), 23.6q (Me on C-2)m 16.4q (Me on C-6).

15. Compound **15** was obtained from cyclohexanone and compound **13** under the same conditions as **12**; orange oil; $C_{20}H_{18}N_2$ (m/z 286), δ_H ($CDCl_3$), 8.05d (J=8.2 Hz), 7.29m (3H), 6.94m (2H), 3.11t (J=6.0, 2H), 3.04t (J=6.0, 2H), 2.36s (Me), 1.89m (2H), 1.66m (2H).

(Received in UK 25 June 1992)