Commun. Fac. Sci. Univ. Ank. Series B
V. 39. pp. 1-9 (1993)

NOVEL SYNTHESIS OF 7-CHLORO-1,6-DIKETOJULOLIDINE FROM METHYL 3-N (3-CHLOROANILONO) PROPIONATE

* E.S. IBRAHIM, M.O.A. ORABI,

Suez Canal University, Faculty of Science, Ismailia, Egypt.

M. EL-BADAWI,

Tanta University, Tanta, Egypt.

M.T. OMAR,

National Research Centre, Dokki, Cairo, Egypt.

(Received Sept. 14, 1990; Accepted Feb. 3, 1993)

ABSTRACT

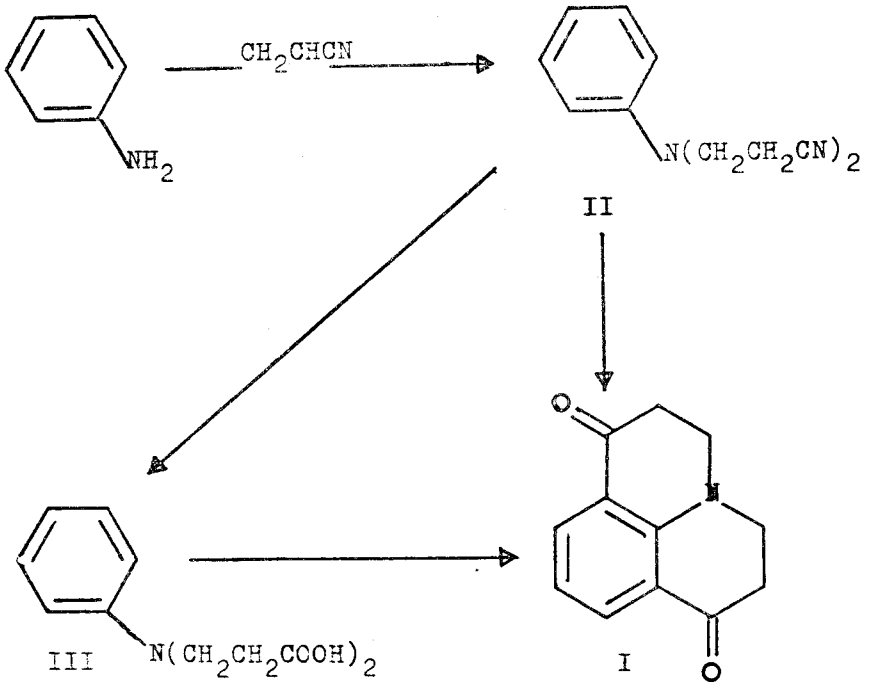
Hydrolysis of methyl 3-N (3-chloroanilino) propionate (VI) gave 3-N (3-chloroanilino) propionic acid (VII) which cyclised to 7-chloro-1, 2, 3, 4-tetrahydro-4-quinolone (V) and 7-7-chloro-1, 6-diketojuloidine (IV). The latter compound also prepared by cyclisation of 3-chloroanilino-N, N-3-bisdipropionic acid (XI) produced through hydrolysis of the diester (XII).

INTRODUCTION

The importance of julolidine and its derivatives were discovered long ago, since it is used in photosensitisers, (1a, b, 2) dyes for: photographic emulsions(3), photographic developers (4) and synthetic fibers(5). Dyes containing the julolidyl group analogues to Michlers ketones were prepared (6). It is also used for aminoacid detection. (7)

Reactivity of some substituted julolidines had been studied by Mann et al(8), they prepared 1,6-diketo-julolidine (I) by cyanoethylation of aniline (and some of its derivatives), the produced N,N-2-biscyanoethylaniline (II) either cyelised to give I or hydrolysed to the corresponding anilino-N, N-3-bisdipropionic acid (III) and then cyclised to 1,6-diketojulolidine (I), cf. scheme 1.

* To whom correspondence should be addressed.



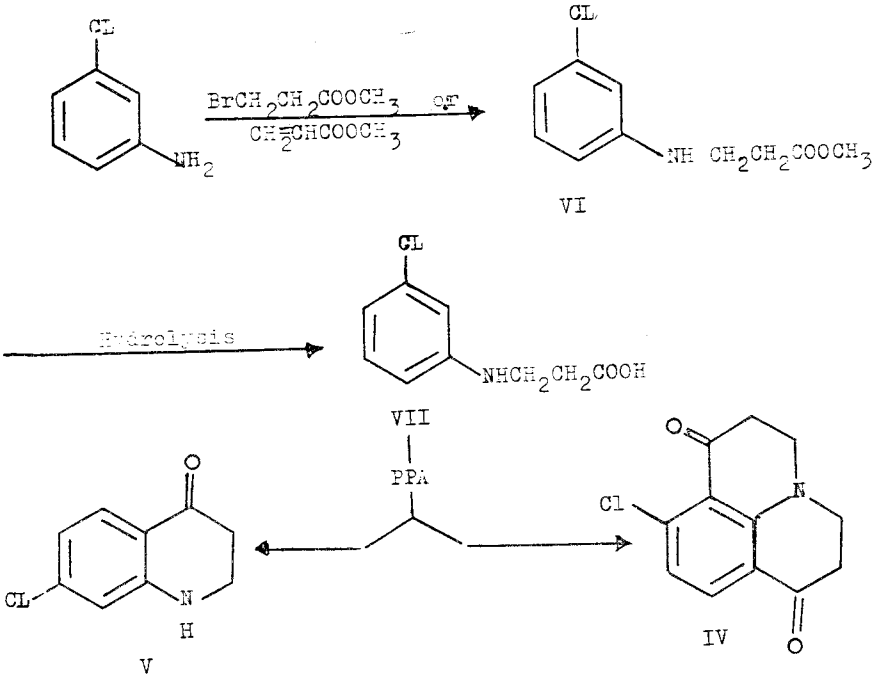
scheme 1

Results and discussion

The formation of 7–chloro–1,6–diketojulolidine (IV) as a by product during the synthesis of 7–chloro–1, 2, 3, 4–tetrahydro–4–quinolone (V)(9) interested us to study this reaction.

Preparation of compound V starting with the commercialy available 3-chloroaniline and / or methyl acrylate, methyl 3–bromopropionate in molar ratios afforded methyl 3–N (3–chloroanilion) propionate (VI), the latter product was hydrolysed to 3–N (3–chloroanilino) propionic acid (VII). Compound VII was cyclised with polyphoshoric acid to give a mixture of IV and V, cf. scheme 2.

The formation of IV from VII could be proposed as follows: In the acid catalysed cyclisation of 3–N (3–chloroanilino) propionic acid (VII), the compound accepts one proton to form the corresponding cation VIII which then decomposes into aniline and 3–propionic acid cation (IX). The latter cation IX either / or;



Scheme 2.

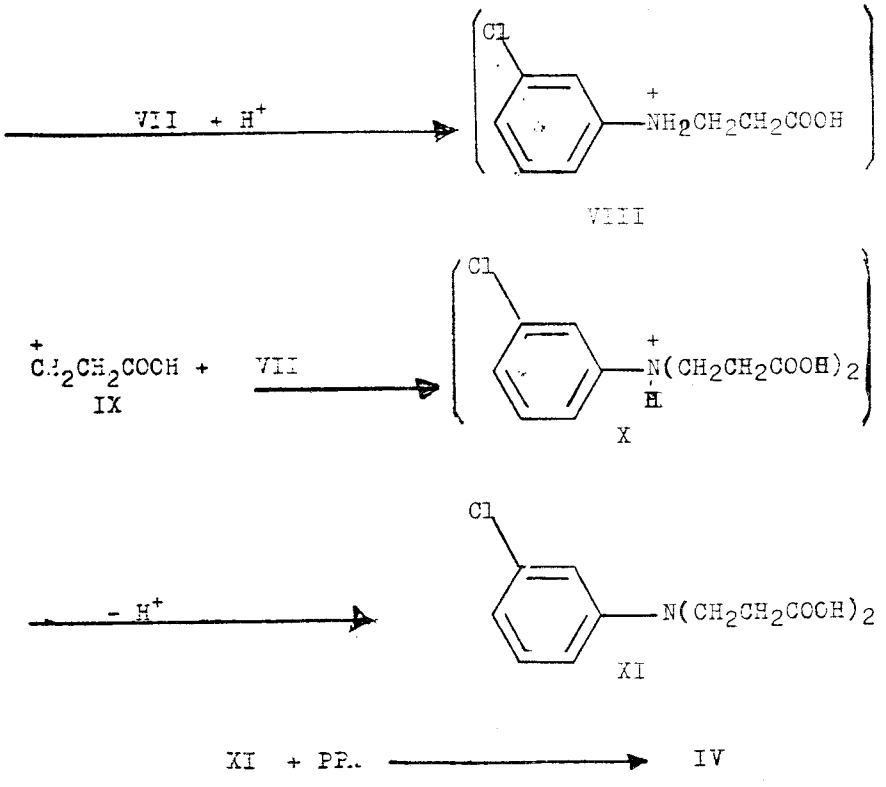
a) Combines with another molecule of 3–N (3–chloroanilino)–propionic acid (VII) to give 3–chloroanilino–N,N–3–bisdipropionic acid cation (X) which then cyclises to 7–chloro–1,6–diketojulolidine (IV), cf. scheme 3.

This scheme is acceptable in the synthesis of I(8), also acceptable in the synthesis of IV as follows:

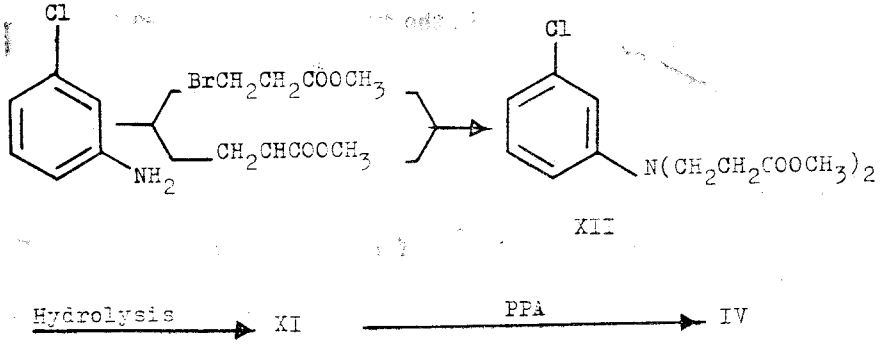
3–Chloraniline condensed with two molecules of etither / or methyl acrylate, methyl 3–bromopropionate to give dimethyl 3–chloroanilino–N, N–3–bisdipropionate (XII), the latter compound was then hydrolysed to XI and cyclised to the target compound IV, cf. cheme 4.

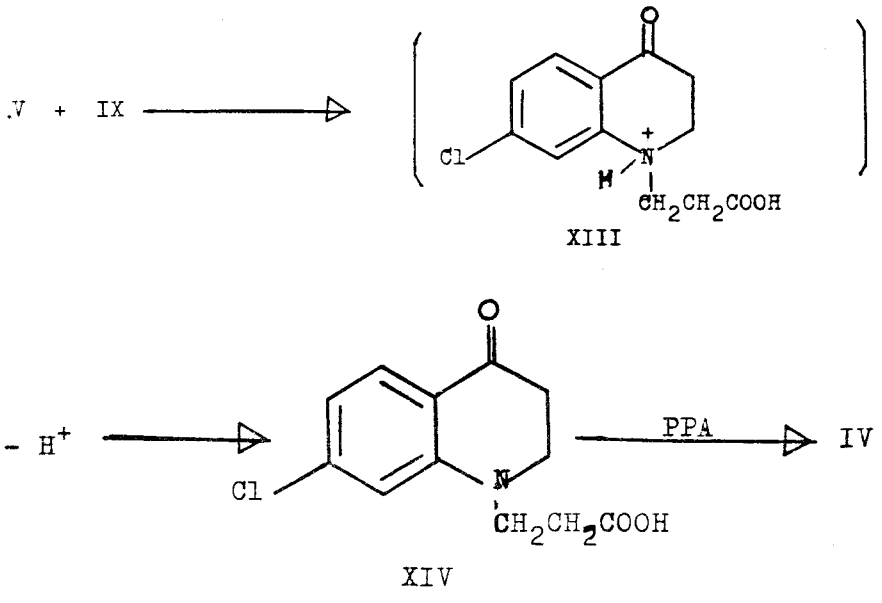
b) Combines with a molecule of 7–chloro–1, 2, 3, 4–tetrahydro–4–oxoquinoline (V) to give 7–chloro–1, 2, 3, 4–tetrahydro–4–quinolono –1– (3–propionic acid) cation (XIII) which cyclises to IV, cf. scheme 5.

Scheme 5 supported by the reported synthesis of 1–ketojulolidine (XV) via condensation of vinyl cyanide with 1, 2, 3, 4–tetrahydroquinolines(8), the produced 1–cyanoethyl–1, 2, 3, 4–terahydroquinoline


VII + H+
Cl
+
NH2CH2CH2COOH
VIII
+
CH2CH2COOH +
IX
VII
Cl
+
N(CH2CH2COOH)2
H
X
- H+
Cl
N(CH2CH2COOH)2
XI
XI + PPA
IV

scheme 3


Cl
BrCH2CH2COOCH3
CH2CHCOOCH3
NH2
Cl
N(CH2CH2COOCH3)2
XII
Hydrolysis
XI
PPA
IV



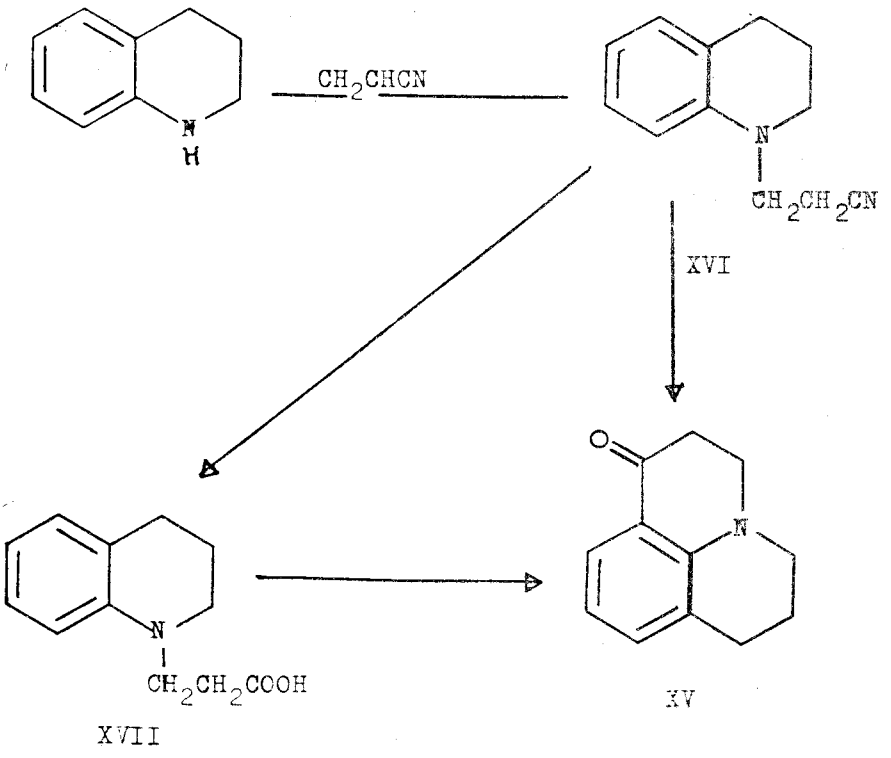
(XVI) either cyclised to XV or hydrolysed to 1, 2, 3, 4–tetrahydroquinolino–1–(3–propionic acid) (XVII) which cyclised to XV, cf. scheme 6.

Experimental

All melting points were uncorrected and were taken in a Galenkamp electric melting point apparatus and Baetius melting point microscope. Elemental analyses were performed by the Microanalytical Laboratory, National Research Centre, Cairo, Egypt. IR spectra were performed on Carl–Zeiss Jena Infrared Spectrophotometer model UR 10 using potassium bromide disk and nujol mull. ^1H NMR spectra were obtained in deuteriotrifloroacetic acid or deuteriochloroform solutions with a Varian Associates model "A–60" spectrometer.

Methyl 3–*N* (3–*chloroanilino*) *propionate* (VI)

Method a): A mixture of 3–chloroaniline (127.5 g., 1 mole), methyl acrylate (86 g., 1 mole) and stannic chloride (4 drops) was refluxed for six hours, the product was distilled under reduced pressure to give compound VI (200 g., 93.6 %) which left to solidify and then crystallised from benzene / light petrol (40–60), m.p. 38°C.



Calcd for: $C_{10}H_{12}ClNO_2$: C, 56.20; H, 5.62; N, 6.56 %

Found: C, 55.97; H, 5.52; N, 6.55 %.

^{1}H NMR ($CDCl_3$) showed: δ 2.56 (2H, t, $-CH_2-$), 3.35 (2H, t, $-CH_2-$), 3.38 (3H, s, $-CH_3$), 4.22 (1H, s, exchangable, –NH–) and 6.35–7.15 (4H., m, aryl).

Method b): A mixture of 3–chloroaniline (127.5 g., 1 mole), methyl 3–bromopropionate (166 g., 1 mole) and sodium carbonate (42 g., 0.05 mole) was refluxed for six hours, after cooling, the mixture was extracted with chloroform, which was dried (Na_2SO_4) and evaporated, the residue was distilled and the title compound collected was (195 g., 91 %), the product was identical with the sample prepared by method (a), TLC, IR, NMR and mixed m.p.

3-N (3-*chloroanilino*) *propionic acid* (VII):

Methyl 3-N (3-chloroanilino) propionate (VI) (60 g., 0.28 mole) was heated for fifteen minutes at 65°C with sodium hydroxide (200 ml., 10 % soln.) and ethanol (20 ml.) then allowed to stand overnight at room temperature. After extraction with benzene, the aqueous layer was acidified and extracted with chloroform which was dried (Na_2SO_4) and evaporated yielding oily product (50 g., 89 %).

Calcd. for: $C_9H_{10}ClNO_2$: C, 54.13; H, 5.01; N, 7.01 %.

Found: C, 54.00; H, 4.97; N, 6.98 %.

^1H NMR ($CDCl_3$) showed: δ 2.56 (2H, t,-CH_2-), 3.35 (2H, t,-CH_2-), 3.83 (1H, s, exchangable, -NH-), 6.4-7.0 (4H, m, aryl) and 8.1 (1H, s, exchangable, -OH carboxylic).

7- *Chloro*-1, 2, 3, 4-*tetrahydro*-4-*quinolone* (V)(9):

3-N (3-chloroanilino) propionic acid (VII) (50 g., 0.2506 mole) was heated at 135°C for ninety minutes with PPA (250 g.; phosphoric acid 100 g. + phosphorous pentaoxide 150 g.) with vigorous stirring, the reaction mixture poured while hot onto ice / water, neutralised with dilute sodium hydroxide, extracted with chloroform, dried (Na_2SO_4), evaporated to give oily product (35 g.). The product was chromatographed on alumina (neutral) and eluted with chloroform to give solid product (mp. 80°C), on successive crystallisation from ethanol compound V was obtained (12.8 g., 28.13 %), mp. 128°C.

Calcd. For: C_9H_8ClNO: C, 59.50; H, 4.40; N, 7.71 %.

Found: C, 59.71; H, 4.52; N, 7.73 %.

^1H NMR ($CDCl_3$) showed: δ 2.66 (2H, t,-CH_2-), 3.55 (2H, t, -CH_2-), 4.65 (1H, exchangable, -NH-) and 6.68-7.8 (3H, m, aryl).

7- *Chloro*-1, 6-*diketojulolidine* (IV):

Method a): The combined filtrates from the successive crystallisation of the solid prouct (mp. 80°) in the previous experiment was concentrated and rechromatographed to give 2.5 g. of IV.

Calcd. for: $C_{12}H_{10}ClNO_2$: M 235.0402, C, 61.14; H, 4.24; N, 5.94 %.

Found: M^+235.0400, C, 61.22; H, 4.38; N, 6.00 %.

^1H NMR ($CDCl_3$) showed: δ 2.85 (4H, t,-CH_2-), 3.55 (4H, t, -CH_2-), 6.8 (1H, d, aryl) and 7.93 (1H, d, aryl).

Dimethyl 3–chloroanilino–N, N–3–bisdipropionate (XII):

Method a): 3–Chloroaniline (64.0 g., 0.5 mole), methyl acrylate (129 g., 1.5 mole) and titanium tetrachloride (5 ml.) were refluxed for one week. On distillation the product collected at (185°C / 0.03 m.m,) was (37 g., 24.66 %).

Calcd. for: $C_{14}H_{18}ClNO_4$: C, 56.09; H, 6.01; N, 4.67 %.

Found: C, 56.71; H, 6.13; N, 4.70 %.

^1H NMR ($CDCl_3$) showed: δ 2.6 (4H, t, $-CH_2-$), 3.78 (4H, t,-$-CH_3-$), 3.8 (6H, s, $-CH_2$) and 6.5-7.25 (4H, m, aryl).

Method b): 3–Chloroaniline (64.0 g., 0.5 mole), methyl 3–bromopropionate (166 g., 1 mole) and sodium carbonate (84 g., 1 mole) were heated at 120°C for twelve hours after which the mixture was extracted with chloroform, dried (Na_2SO_4), evaporated to leave (105 g., 70 %) which was identical with the sample prepared by method (a), TLC, IR, and NMR.

3– *Chloroanilino–N, N–3–bisdipropionic acid* (XI):

The previous ester XII (12 g., 0.04 mole), sodium hydroxide (50 ml., 20 %) and ethanol (20 ml.) were heated on a water bath for fifteen minutes and left overnight at room temperature, then diluted with water and extracted with chloroform. The aqueous layer was acidified (dil. HCl), after thirty minutes the title acid XI was separated, collected, washed and dried to give (5 g., 46.29 %), mp. 140°C.

Calcd. for: $C_{12}H_{14}ClNO_4$: C, 53.03; H, 5.15; N, 5.15 %.

Found: C, 52.97; H, 5.23; N, 5.10 %.

^1H NMR ($CDCl_3$) showed: δ 2.55 (4H, t, $-CH_2-$), 3.6 (4 H, t, $-CH_2-$), 4.23 (2H, s, exchangable, –OH carboxylic) and 6.6–7.3 (4H, m, aryl).

7– *Chloro*-1, 6–*diketojuloridine* (IV):

The foregoing acid XI (1 g., 0.0036 mole) was heated at 140°C with phosphoric anhydride (10 g., 80 %) for two hours after which the mixture was poured onto ice / water, extracted with chloroform, dried (Na_2SO_4), evaporated to give (0.2 g., 23 %), mp. 156°C. The product was identical with the sample obtained as by product in experiment IV, TLC, IR, NMR, mass spectra and mixed m.p.

REFERENCES

1a. P.I. ITTYERAH and F.G. MANN; J. Chem. Soc. 1956, 3179.

b. "Fundamental Mechanisms of Photographic Sensitivity" Bristol Symposium, Butterworth, London, 1951, pp 168–172.

2. P.I. ITTYERAH and F.G. MANN; J. Chem. Soc. 1958, 467.

3. D.W. HESELTINE and L.L. LINCOLN, (to Eastman Kodak Co.) U.S. Patent 3. 049, 418 (Cl. 96–84) Jan 18, 1963, Appl. Mar. 10, 1960, 6 pp (cf. Chem. Abst. 60: 3136 (1964).

4. S. MAYNARD, Raash (to E.I. du Pont de Nemours and Co.) U.S. Patent 2. 707, 681 May 3, 1955 (cf. Chem. Abst. 50: 717e (1956)).

5. L.G.S. BROKER and D.W. HESELTINE, (to Eastman Kodak Co.) U.S. Patent 2. 666, 761 Jan. 19, 1954 (cf. Chem. Abst. 49: 757f (1955)).

6. R.W. CASTELLINO and G. HALLAS; J. Chem. Soc. (B) 1971, 1468.

7. W.H. DREVENY and W.E. ZİEGLER; Monatsh. Chem. 99 (4), 1543–50 (1968) (Ger.).

8. F.G. MANN and B.B. SMITH; J. Chem. Soc. 1951, 1868.

9. E.S. IBRAHIM, A.M. MONTGOMERIE, A.H. SNEDDON, G.R. PROCTOR and B. GREEN; Eur. J. Med. Chem. 23, (1988), 183.