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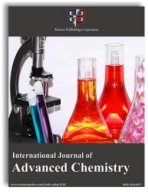


Synthesis of Nitrogen-Containing Chalcone Via One-Pot Three-Component Reaction . part ii

M. J. A. Abualreish [1, 5]*, Anwar E. M. Nor E. Ljaleel [1], Himat M. A. Fadul [1], Saad M. H. Ayuob [2], M, Abdel Karim [3], Jan H. Van Der Westhuizen [4]

[1] Department of Chemistry, Faculty of Science, Omdurman Islamic University, Khartoum- Sudan
[2] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, El-Neeilain University , Khartoum
[3] Departments of Chemistry, Sudan University of Science and Technology, Faculty of Science, Khartoum- Sudan
[4] Department of Chemistry, Faculty of Agriculture and Science,, University of Free state, Bloemfontein-South Africa
[5] Department of Chemistry, Faculty of Science, Northern Border University, Arar, Kingdom of Saudi Arabia
**Corresponding author E-mail: Mustjeed_2008@hotmail.com*

Abstract

The compound 3-Hydroxy-4'-methoxychalcone (1) was prepared by reacting 3-hydroxybenzaldehyde with 4-methoxyacetophenone. The aminomethylation of this chalcone was accomplished by reaction with formaldehyde and N-methylpiperazine in dry acetonitrile to Obtain 3-hydroxy-4'-methoxy-4-(N-methyl-piperazinomethyl) chalcone (2) and 3-hydroxy-4'-methoxy-2,4-bis-(N-methylpiperazinomethyl)chalcone(3). The products were purified by column and thin layer chromatography and were identified along with their intermediates by spectroscopic methods: UV, IR, NMR and mass spectrometry.

Keywords: *Chalcone; 3-Hydroxybenzaldehyde; 4-Methoxyacetophenone; Aminomethylation; Formaldehyde ; N-Methylpiperazine.*

1. Introduction

Mannich reaction is a condensation reaction between (i) ammonia , primary or secondary amines (ii) an active hydrogen compound and (iii) formalin .The product of such condensation is known as a Mannich base.

Studies on the chemistry of Mannich bases are of interest in various areas of applications. A large number of aminoalkyl derivatives have been synthesized in order to correlate their structure and reactivity with their pharmacological potential. Also Mannich bases represent easily obtainable intermediates for the synthesis of other compounds such as heterocycles, aminoalcohols …etc.

Chalcones, which are considered to be precursors of flavonoids, are abundant in edible plants. Chemically , they are open chain flavonoids in which the two aromatic rings are joined by a three-carbon α ,β-unsaturated carbonyl function.

Mannich bases are known for their biological potential. Some Mannich bases posses anticonvulsant (Mutlu & Vnsal 2007) , (Ozan et. al 2005), analgesic (Nabil et.al 1993), cytotoxic (Robert et.al 2006), (Ina-Gull et.al 2000), (Ebru et.al 2007), (Jontathan et.al 2002). Antimalarial (Stephen et.al 1987), antibacterial (Tamas et.al 2002), antimicrobial (Afaf et.al 2000) and anticancer activity (Janathan et.al 1998), (Dimmock & Kamar 1997). Chalcones exhibit diverse pharmacological activities, including anti- inflammatory (Abraham et. al 2003), (Herencia et. al 1998), antimitotic (Ko et.al 2003), antitubercolosis(Lin et. al 2002), antifungal(Lopez et. al 2001), antimalarial. (Li et. al 1995), (Parmer et. al 2003) properties.

Bearing such interesting properties of Mannich bases and chalcones in mind, it was decided to join Mannich bases and chalcones in one molecule , probably which potential pharmacological activities. The target molecule is approached via effective and facile strategy involving synthesis of chalcones and subsequent aminomethylation.

2. Experimental

2.1. Instruments

IR spectroscopy was carried out using Spectrum BX instrument model L1050033, UV/VIS spectroscopy was carried out using Beckman Coulter instrument model DU 800 Spectrophotmeter.

NMR spectroscopy was carried out using Procker instrument model AvanceII 600 and using Procker instrumen AvanceII 300 and MS spectroscopy was carried out using MDS SCIEX instrument modelAPI 2000 LC/ MS/MS System.

2.2. Synthesis of 3-hydroxy-4'-methoxychalcone (1)

10 ml of 10% sodium hydroxide solution were added to a solution of the 4-methoxyacetophenone (0.02 mol) and 3-hydroxybenzald--ehyde (0.02 mol) in ethanol (6 ml) .The mixture was stirred at room temperature for 24 h and poured into water (100 ml). After neutralization with 10% hydrochloric acid a yellow solid was obtained. m.p 150-153 ^{O}C (yield 80%).

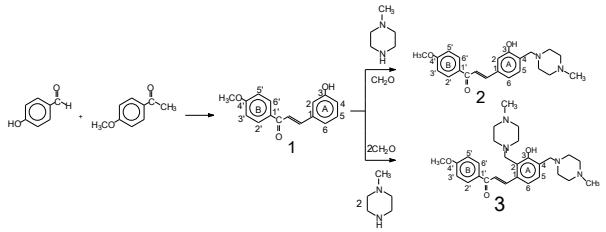
2.3. Synthesis of Chalcone substituted with Mannich side chain

A mixture of 3-hydroxy-4'-methoxychalcone(1) (0.005 mol) , formalin (0.01 mol) and N-methylpiperazine (0.01 mol) were

reacted in dry acetonitrile (50 ml) and heated under reflux for 36 h. On cooling a precipitate was formed and the crude products were fractionated on silica gel G using the solvent system: hexane/ethylacetatel/methanol 6:3:1 .Two products were obtained 3-hydroxy-4'-methoxy-4-(N-methylpiperazinomethyl) chalcone(**2**) as pale yellow crystals, m.p136-137 ^{O}C, (yield 60%) and 3-hydroxy-4'-methoxy-2, 4-bis-(N-methylpiperazinomethyl) chalcone (**3**) also as pale yellow crystals, m.p 122-123 ^{O}C, (yield 58%).

3. Results and discussion

3-hydroxy-4'-methoxychalcone (**1**) was prepared according to the procedure outlined above , and also two other chalcones with Mannich side chain (**2**) and (**3**) were prepared together with their intermediate according to the following scheme **:**



The UV spectrum of compound (1) (Fig (1) a) showed λ_{max} (etha--nol), 260, 310 and 386 nm due to the benzoyl and cinnamoylchromophores. The IR spectrum ν(KBr) (Fig (1) b) showed 831 (C-H, Ar, bending), 1168.7 (C-N) 1263 (C-O), 1510, 1556 and 1591 (C=C, Ar, st,vib), 1650.9 (C=O. st, vib), 2840 (C-H aliphatic), 2966 (C-H Ar) and 3340 (OH) cm^{-1}.The ^{1}H-NMR spectrum of compound (1) (Fig (1) c) showed δ 7.51 (d, 1H, J = 16.6 Hz) and δ 7.73 (d, 1H, J = 16.6 Hz) corresponding to α and β protons respectively. The signal at δ 7.09 (d, J 7.0 Hz, 2H), was assigned for $C_{2',6'}$-H, while the signal at δ 8.15 (d, J 7.0 Hz, 2H), is due to $C_{3',5'}$-H of ring B. The signal at δ 6.95 (m, 1H) was assigned for C_6-H, while the resonance at δ 7.27 (m, 3H) is characteristic of C_2, C_3 and C_4 protons. The mass spectrum of compound (1) (Fig (1) e) gave m/z 255.10132 (100%) (Base peak) for the molecular ion.

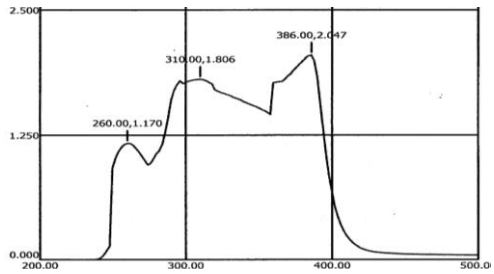


Fig.1, a : UV spectrum of 3-hydroxy-4'-methoxychalcone (1).

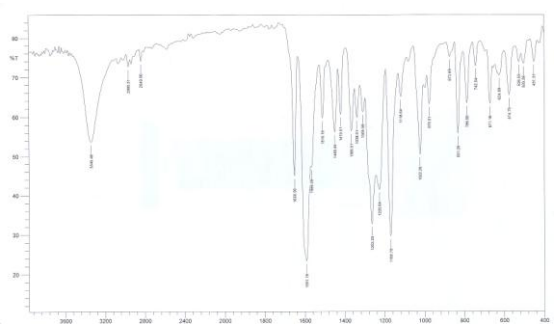


Fig.1, b : IR spectrum of 3-hydroxy-4'-methoxychalcone (1).

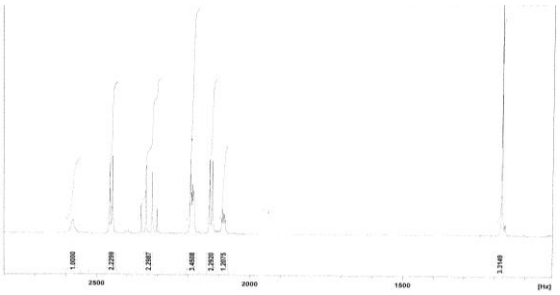


Fig.1, c :^{1}HNMR spectrum of 3-hydroxy-4'-methoxychalcone (1).

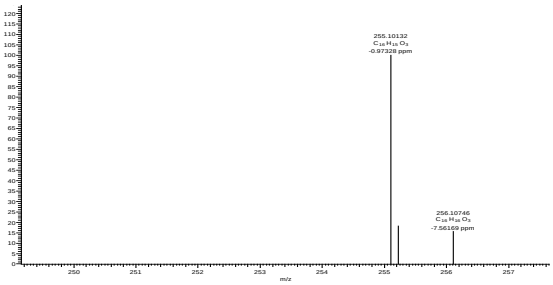


Fig. 1, d :Accurate mass spectrum of of 3-hydroxy-4'-methoxy- - chalcone (1).

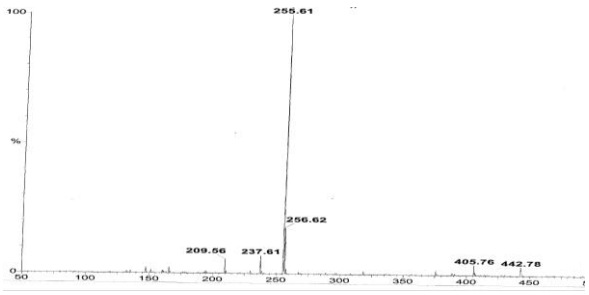


Fig. 1, e :Mass spectrum of 3-hydroxy-4'-methoxychalcone (1).

When 3-hydroxy-4-methoxychalcone, reacted with N-methyl- -piperazine and formalin in dry acetonitrile under reflux 3-hydroxy-4'-methoxy-4-(N-methyl-piperazinomethyl) - -chalcone(2) was obtained m.p136-137 ^{O}C , (60%). The UV spectrum (Fig (2) a) gave λ_{max} (ethanol) 260, 320, 335 and 385 nm. The IR spectrum ν (KBr) (Fig (2) b) showed 827 (C-H, Ar, bending), 1164 (C-N), 1265 (C-O), 1450, 1510, 1602 (C=C, Ar, st,vib), 1654 (C=O. st, vib), 2765, 2794 (C-H, aliphatic), 2840 (C-H, Ar) and 2931 cm^{-1} (OH). The ^{1}H-NMR spectrum (Fig (2) c) showed a singlet at δ 2.32 (3H) assigned for the methyl group. The multipletcentered at δ 2.40 was assigned for the 8 protons of the N-methylpiperazine ring. The signal at δ 3.75 (s, 2H), is characteristic of $\gtrless N-CH_2-$ whilst the singlet at δ 3.89 was assigned for the methoxy group.

The resonance at δ 6.98 (d, J = 8.8 Hz, 2H) was assigned for $C_{3'}$ and $C_{5'}$-H. The resonate at δ 8.03 (d, J = 8.8 Hz, 2H) was assigned for $C_{2'}$ and $C_{6'}$-H. The doublet at δ 7.51 (J = 15.6,1H) was assigned for β-H and the signal δ 7.73 (J = 15.6, 1H) for the α–H. The doublet at δ 7.00 (1H, $J_{6,5}$7.7 Hz,) was assigned to C_5-H, the signal centered at δ 7.13 (dd, $J_{6,5}$ 7.7 Hz, $J_{2,6}$ Hz1.6 1H) was assigned for the C_6-H, while the resonance at δ 7.15 (d, $J_{5,6}$ 1.6 Hz 1H) was assigned for C_2-H. ^{1}H-^{1}H cosy NMR (Fig (2) e) demonstrated a diagonal relationship between β-H (δ 7.15), and α-H (δ 7.73). ^{13}C NMR spectrum (Fig (2) f) showed a C_{22} system. The mass spectrum (Fig (2) g) showed m/z 267.4 (60%) for the molecular Ion. Other fragment at m/z 101 (100%) (Base peak) and m/z 267.1 (50%) is due to loss of amino group. The fragment at m/z 239.0 (80%) is due to loss of the amine group and carbon monoxide.

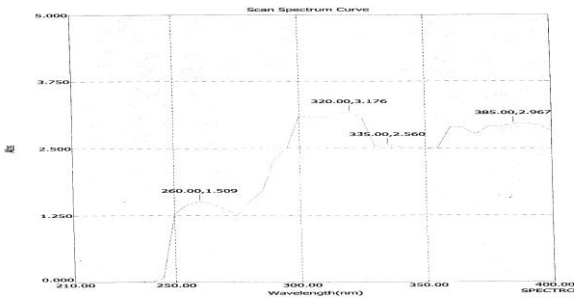


Fig. 2, a :UV spectrum of 3-hydroxy-4'-methoxy-4--(N-methylpiperazinomethyl) chalcone (2).

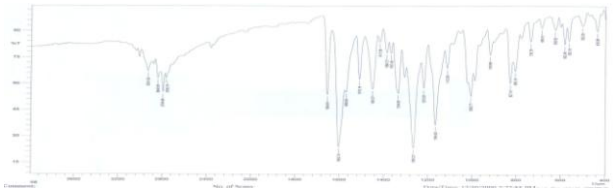


Fig. 2, b :IR spectrum of 3-hydroxy-4'-methoxy-4--(N-methylpiperazinomethyl) chalcone (2).

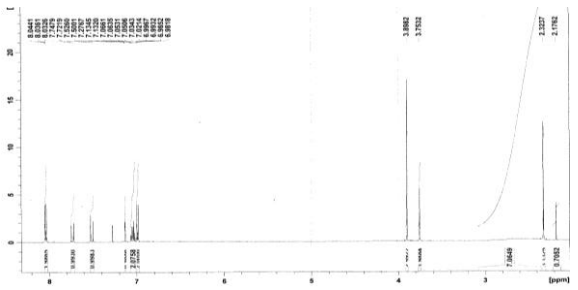


Fig. 2, c : ^{1}H-NMR spectrum of 3-hydroxy-4'-methoxy-4--(N-methylpiperazinomethyl) chalcone (2).

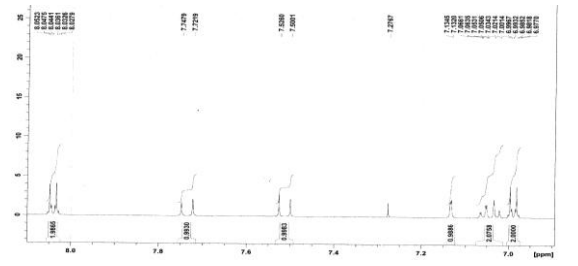


Fig. 2, d :^{1}H-NMR spectrum of 3-hydroxy-4'-methoxy-4--(N-methylpiperazinomethyl) chalcone (2).

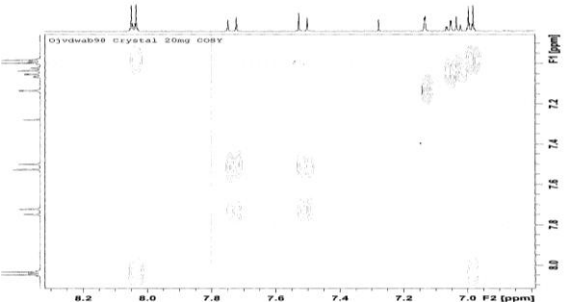


Fig. 2, e :^{1}H-^{1}H cosy NMR of 3-hydroxy-4'-methoxy-4--(N-methylpiperazinomethyl) chalcone (2).

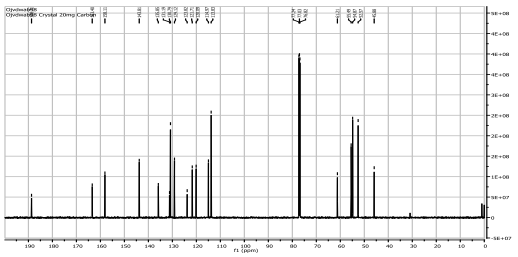


Fig. 2, f : ^{13}C-NMR spectrum of 3-hydroxy-4'-methoxy-4--(N-methylpiperazinomethyl) chalcone (2).

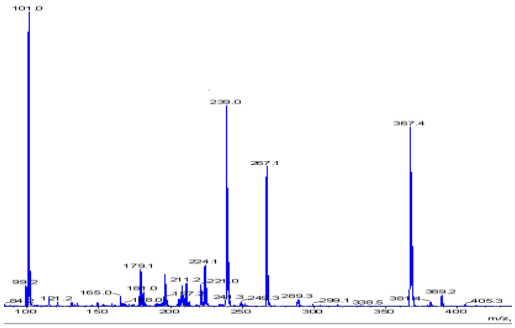


Fig. 2, g : Mass spectrum of 3-hydroxy-4'-methoxy-4-(N-methyl--piperazinomethyl) chalcone (2).

When 3-hydroxy-4'-methoxychalcone, reacting with N-methylpiperazine and formalin in dry acetonitrile under reflux, 3-hydroxy-4'-methoxy-2, 4-bis-(N-methylpiperazinomethyl) chalcone (3) was obtained m.p 122-123 ^{O}C, (58%).

The UV spectrum (Fig (3) a) showed λ_{max} (ethanol) 260, 320, 335 and 385 nm. The IR spectrum ν(KBr) (Fig (3) b) showed 827 (C-H, Ar, bending), 1164 (C-N), 1265 (C-O), 1450, 1510, 1602 (C=C, Ar, st,vib), 1654 (C=O. st, vib), 2765, 2794 (C-H, aliphatic), 2840 (C-H, Ar) and 2931 (OH) cm^{-1}. The ^{1}H-NMR spectrum (Fig (3) c) showed two singlet at δ 2.26 (3H), δ 2.29 (3H) assigned for the two methyl groups. The two multiplets at δ 2.39-2.49 (8H), and δ 2.49-2.68 (8H) were assigned for the protons of two N-methylpiperazine rings. The two methylene groups $\rangle N-CH_2-$ appeared as singlets at δ 3.67, and δ 3.80. The methoxy group resonates at δ 3.89. The resonance at δ 7.35 (d, 14.5 Hz, 1H), was assigned for C_{β}-H, while the doublet at δ 8.15 (14.5 Hz, 1H) was assigned for C_{α}–H. The doublet at δ 7.04 (J6, 57.7 Hz, 1H) is characteristic of C_5-H, while the signal at δ 7.15 (d, $J_{5,6}$ 7.7 Hz 1H) is characteristic of C_6-H. The doublet at δ 7.00 (d, 8.8Hz, 2H) was assigned for $C_{3'}$ and $C_{5'}$-H, while the signal at δ 8.14 (d, 8.8 Hz, 2H) was assigned for $C_{2'}$ $C_{6'}$-H. ^{13}C NMR spectrum (Fig (3) e) showed a C_{28} system. Apt experiments(Fig (3) f) showed 11 carbons in negative mode (one OCH_3, two Me and eight =CH-), and 17 carbons in positive mode (ten CH_2-, and seven quaternary carbons).

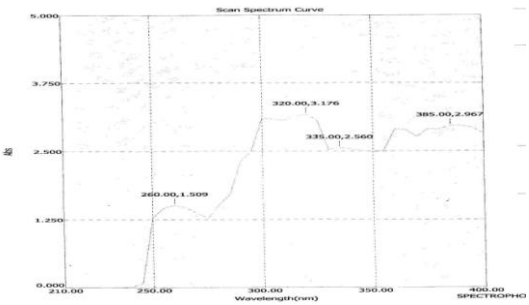


Fig. 3, a : UV spectrum of 3-hydroxy-4'-methoxy-2,4-bis-(N--methylpiperazinomethyl) chalcone (3).

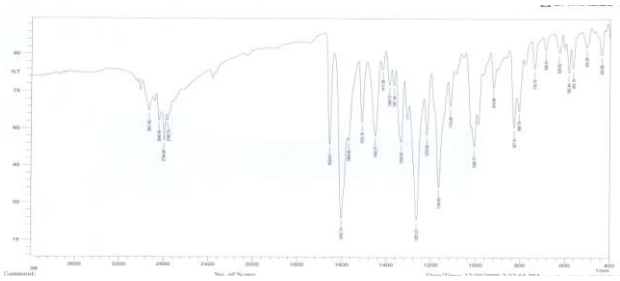


Fig. 3, b : IR spectrum of 3-hydroxy-4'-methoxy-2,4-bis-(N--methylpiperazinomethyl) chalcone (3).

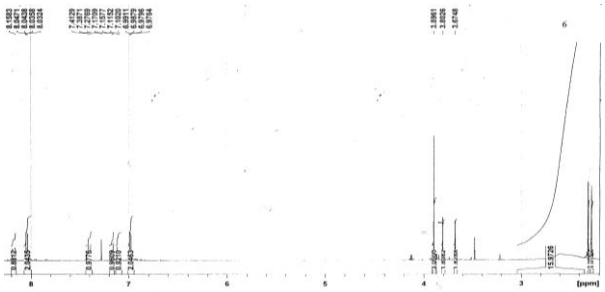


Fig. 3, c: ^{1}H-NMR spectrum of 3-hydroxy-4'-methoxy-2,4-bis-(N--methylpiperazinomethyl) chalcone (3).

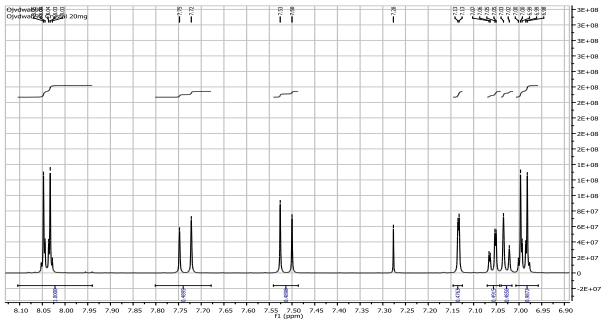


Fig. 3, d:^{1}H-NMR spectrum of 3-hydroxy-4'-methoxy-2,4-bis-(N--methylpiperazinomethyl) chalcone (3).

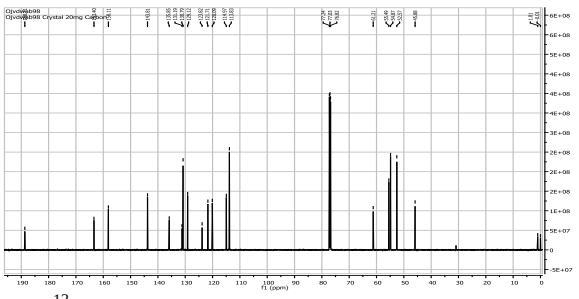


Fig. 3,e: ^{13}C-NMR spectrum of 3-hydroxy-4'-methoxy-2,4-bis-(N--methylpiperazinomethyl) chalcone (3).

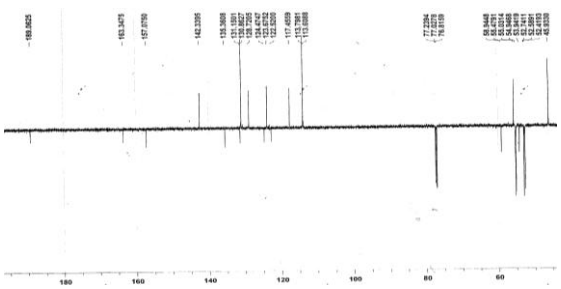


Fig. 3, f : Apt experiments of 3-hydroxy-4'-methoxy-2, 4-bis-(N--methylpiperazinomethyl) chalcone (3).

4. Conclusion

The aminomethylation of chalcone by reaction with formaldehyde and suitable amine in acetonitrile was achieved and characterization of the products and their intermediates by spectroscopic methods: UV, IR, and NMR and mass spectrometry were discussed.

Acknowledgements

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