Indian Journal of Chemistry
Vol. 26B, June 1987, pp. 594-595

4-Keto-4,5,6,7-tetrahydrooxindoles & 1-Carboxymethylene-2-anilino-1-cyclohexen-6-ones with Potential Antiinflammatory Activity†

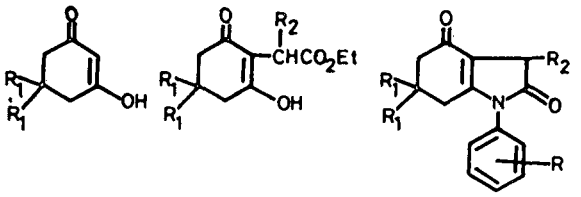
K NAGARAJAN*‡ & S J SHENOY‡
Hindustan CIBA-GEIGY Ltd., Research Centre, Bombay 400 063

Received 6 *October* 1986; *accepted* 6 *November* 1986

1-Aryl-4-oxo-4,5,6,7-tetrahydroindoles (**1-16**) have been synthesised by the condensation of cyclohexane-1,3-dione-2-acetic esters with anilines. Hydrolysis of **1-16** affords the corresponding acids (**17-32**), bearing resemblance to the nonsteroidal antiinflammatory agent, diclofenac **38**. Some members of both classes show antiinflammatory activity in the carragenin oedema test and analgesic activity in mouse writhing test, but are devoid of prostaglandin synthetase inhibiting property. Among these, 1-carboxymethylene-2-(4-trifluoromethylanilino)-1-cyclohexen-6-one (**20**) has marginal activity in the chronic adjuvant arthritis model of inflammation.

The phenomenal success of diclofenac (**38**) as a nonsteroidal antiinflammatory agent[1] and the recent publication of a Japanese patent[2] for a new process for its manufacture prompts us to record results of a very similar project we had recently completed.

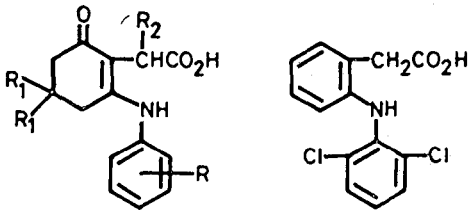
As part of our exercises to build heterocycles onto cyclohexane-1,3-diones[3,4] for diverse biological activities[5-7], we synthesised several 4-oxo-4,5,6,7-tetrahydrooxindoles (**1-16**) in 40-60% yield by the reaction of anilines with acetic acid esters (**35-37**) which were available from the known[8] alkylation of cyclohexane-1,3-diones (**33** and **34**) by ethyl α-bromoacetate of α-bromopropionate, respectively. Exposure of **1-16** to hot aq sodium bicarbonate led to the corresponding, soluble sodium salts of acids (**17-32**) in yields around 80%. Physical data for the two series are presented in Tables 1 and 2. All new compounds were properly characterized by microanalytical data (C,H,N) and structures were supported by spectral data.



33 R_1 = H
34 R_1 = Me

35 $R_1 = R_2 = H$
36 R_1 = Me, R_2 = H
37 R_1 = H, R_2 = Me

1-9 $R_1 = R_2 = H$
10-14 R_1 = Me, R_2 = H
15, 16 R_1 = H, R_2 = Me



17-25 $R_1 = R_2 = H$
26-30 R_1 = Me, R_2 = H
31-32 R_1 = H, R_2 = Me

38

It was our initial objective to aromatise the 2,6-dichlorophenyl derivative **25** to diclofenac, but we were sidetracked by the observation of some antiinflammatory-analgesic activities for a few members of the study. The screening consisted of the following routine tests: Prostaglandin synthetase inhibition *in vitro*; and inhibition of carragenin foot oedema in rats and inhibition of writhing syndrome induced by phenyl-p-benzoquinone in mouse. A very small number of active compounds were also subjected to the following tests: Leukotriene B_4 inhibition *in vitro*; and arachidonic acid lung embolism and adjuvant arthritis in rabbit. These tests were carried out according to routine protocols[1,9,10].

Table 1—1-Aryl-4-oxo-4,5,6,7-tetrahydrooxindoles (**1-16**)

Compd	R	Mol. formula	Crystallised from*	m.p. °C
1	H	$C_{14}H_{13}NO_2$	A+C	136-38
2	3-CF_3	$C_{15}H_{12}F_3NO_2$	F+D	132-34
3	4-Cl	$C_{14}H_{12}ClNO_2$	F+C+D	118-20
4	4-CF_3	$C_{15}H_{12}F_3NO_2$	F+C	130-31
5	4-Me	$C_{15}H_{15}NO_2$	F+C	136-38
6	4-F	$C_{14}H_{12}FNO_2$	F+C	156-58
7	4-OMe	$C_{15}H_{15}NO_3$	B+C	98-100
8	2,3-DiMe	$C_{16}H_{17}NO_2$	F+C+D	123-25
9	2,6-DiCl	$C_{14}H_{11}Cl_2NO_2$	F+D	146-48
10	H	$C_{16}H_{17}NO_2$	F+D	182-84
11	2-Me	$C_{17}H_{19}NO_2$	F+C+D	140-42
12	3-CF_3	$C_{17}H_{16}F_3NO_2$	F+D	130-32
13	4-F	$C_{16}H_{16}FNO_2$	F+C	144-46
14	2,3-DiMe	$C_{18}H_{21}NO_2$	F+C+D	154-58
15	3-CF_3		gum	
16	4-F	$C_{15}H_{14}FNO_2$	F+D	158-60

*Solvents for crystallisation: A-Chloroform; B-ethanol; C-ether; D-hexane; E-methanol; F-methylenechloride

†Contribution No. 811 from Research Centre.
‡Present address: R & D Centre, Searle (India) Ltd, Thane Belapur Road, Thane 400 601.

Table 2—Carboxymethylene-2-anilino-1-cyclohexen-6-ones (17-32)

Compd	R	Mol. formula	Crystallised from*	m.p. °C
17	H	$C_{14}H_{15}NO_3$	F+E+C	180-82
18	3-CF_3	$C_{15}H_{14}F_3NO_3$	F+E+C	172-74
19	4-Cl	$C_{14}H_{14}ClNO_3$	F+C	140-42
20	4-CF_3	$C_{15}H_{14}F_3NO_3$	F+E+C	148-50
21	4-Me	$C_{15}H_{17}NO_3$	F+E+C	150-52
22	4-F	$C_{14}H_{14}FNO_3$	F+E+C	132-34
23	4-OMe	$C_{15}H_{17}NO_4$	F+E+C	146-48
24	2,3-DiMe	$C_{16}H_{19}NO_3$	F+C	138-40
25	2,6-DiCl	$C_{14}H_{13}Cl_2NO_3$	F+E+C	180-82
26	H	$C_{16}H_{19}NO_3$	C	200-1
27	2-Me	$C_{17}H_{21}NO_3$	F+C	150-52
28	3-CF_3	$C_{17}H_{18}F_3NO_3$	F+E+C	152-55
29	4-F	$C_{16}H_{18}FNO_3$	F+E+C	205-8
30	2,3-DiMe	$C_{18}H_{23}NO_3$	F+C+D	152-57
31	3-CF_3	$C_{16}H_{16}F_3NO_3$	F+E+C	128-30
32	4-F	$C_{15}H_{16}FNO_3$	F+C	117-20

*For solvents of crystallisation see Table 1.

Among the perhydroxindoles, compound **6** was quite potent in the carragenin oedema test (ED_{40} 30 mg/kg p.o. ≙phenylbutazone) and in the arachidonic acid embolism test. It had peripheral analgesic activity in mouse writhing syndrome test (ED_{50} 40 mg/kg p.o.). On the other hand, it had no *in vitro* activity in the prostaglandin (upto 3000 nona mol/litre) or leukotriene assay. Although these properties could signify an interesting mode of action for **6**[1], lack of activity in the chronic adjuvant arthritis model of inflammation even at 200 mg/kg p.o. rendered it uninteresting as a candidate drug. Among the acetic acids, the 2,6-dichloroanilino derivative **25** was only one-fiftieth as active in the carragenin oedema test ($ED_{40} > 100$ mg/kg p.o) as compared to diclofenac (**38**) ($ED_{40} \approx 2$ mg/kg p.o.). Compound **18** was more active than **25**, but had no analgesic activity or activity in the adjuvant arthritis test. The 4-trifluoromethyl-anilino acid (**20**) had moderate activity in the carragenin oedema test ($ED_{40} \approx 20$ mg/kg p.o.) and good analgesic activity in the mouse writhing test ($ED_{50} \approx 10$ mg/kg p.o.) but had a flat dose-response curve in both the tests. Its inactivity in the *in vitro* prostaglandin synthesis test upto 3000 nonamol/litre in contrast to highly potent **38** (IC_{50} 1.2 nonamol/litre) should have qualified it for further development, since it could signify an interesting mode of action[1]. However, in the critical adjuvant arthritis model of inflammation, **20** had only very weak activity (ED_{40} >100 mg/kg p.o.) compared to **38** (ED_{40} 0.5 mg/kg p.o.), thus disallowing any serious interest in the compound.

2-Carbethoxymethylenecyclohexane-1,3-diones

2-Carbethoxymethylenecyclohexane-1,3-dione (**35**) was prepared by the action of ethyl bromoacetate on cyclohexane-1,3-dione[8].

Compound **36** (m.p.) 105-8°; from methylene chloride-ether) and **37** (m.p. 98-100°; from methylene chloride-ether) were prepared similarly.

4-Oxo-4,5,6,7-tetrahydrooxindoles (**1-16**)

A mixture of **36** (7 g), aniline (3.5 g) and acetic acid (35 ml) was heated under reflux for 16 hr. Acetic acid was removed *in vacuo* and the residue triturated with water to afford **1**.

Similarly were prepared **2-16** (yield 30-60%). In some cases gums were obtained which were chromatographed over silica gel using chloroform containing 2% methanol. The first fractions gave the required compounds and the latter ones gave acetanilides. The physical data and solvent of recrystallisation for **1-16** are given in Table 1.

1-Carboxymethylene-2-anilino-1-cyclohexen-6-ones (**17-32**)

A mixture of **1** (6 g), ethanol (15 ml) and saturated aq sodium bicarbonate (160 ml) was boiled under reflux for 5 hr after which it was cooled and extracted with ether. The organic layer was removed and the aqueous layer carefully acidified to *p*H 4-5 with conc. hydrochloric acid to obtain **17**.

Compounds **18-32** were prepared similarly. The physical data and solvent of recrystallisation for compounds **17-32** are given in Table 2.

The authors wish to thank the CIBA-GEIGY, Basel, for making available screening results of compounds of this study.

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