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Synthesis of 5-Aryl-12*H*-quinazolino[3,2-*a*]quinazolin-12-ones as Antiinflammatory Agents

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Condensation of 4-aryl-2-chloroquinazolines with anthranilic acids leads to 5-aryl-12*H*-quinazolino[3,2-*a*]quinazolin-12-ones. Their mass-spectral fragmentations were studied. Some of these compounds were tested for analgesic and antiinflammatory activities.

Synthese von 5-Aryl-12-H-chinazolino[3,2-a]chinazolin-12-onen als entzündungshemmende Wirkstoffe

Aus der Kondensation von 2-Chlor-4-arylchinazolin mit Anthranilsäuren gehen 5-Aryl-12*H*-chinazolino[3,2-a]chinazolin-12-one hervor. Ihre massenspektrometrischen Fragmentierungswege werden untersucht. Einige Verbindungen zeigen analgetische und entzündungshemmende Wirkungen.

It is known from the literature[1] that quinazolinones possess a broad spectrum of physiological action. Amongst a number of 4(3*H*)-quinazolinones[2], synthesized in this laboratory and tested for biological activity, 2-methyl-3-o-tolyl-4(3*H*)-quinazolinone[3] (Methaqualone) exhibits profound central nervous system depressant action and was the first non-barbiturate hypnotic drug introduced for therapeutic use.

2(1*H*)-quinazolinones have been reported to possess a wide range of biological activity such as analgesic, antiinflammatory[4], uricosuric and antiviral properties. Structure activity studies by *Coombs* et al.[5] in the 2(1*H*)-quinazolinone series led to the synthesis of 1-isopropyl-4-phenyl-7-methyl-2(1*H*)-quinazolinones (Proquazone) which emerged as a very active antiinflammatory com-

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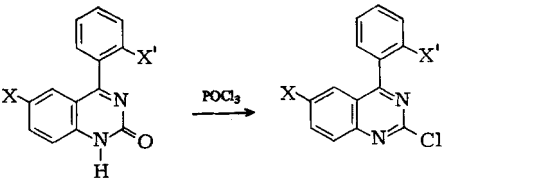
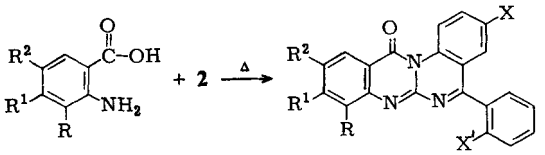
pound. Clinical success of Proquazone[6] and the well documented findings relating to the quinazolinone system prompted us to prepare a series of quinazolino[3,2-a]quinazolin-12-ones with a view to explore their biological profile.

In the course of investigations on the applications of chlorosulfonyl isocyanate, we discovered a new reaction sequence leading to 4-aryl-2(1*H*)-quinazolinones[7] **1**. Reaction of **1** with phosphorus oxychloride gave the corresponding 2-chloro-4-aryl-quinazolines **2**. The condensation of **2** with a variety of anthranilic acids **3** yielded the 5-aryl-12*H*-quinazolino[3,2-a]quinazolin-12-ones **4a–i** given in table 1. These have been characterized by elementary analysis, IR and mass spectra.



1 **2**



3 **4a-i**

Mass Spectra

5-Aryl-12*H*-quinazolino[3,2-a]quinazolin-12-ones have been subjected to electron impact to study their fragmentation pathway. The following salient features are observed in the mass spectrum of **4a**.

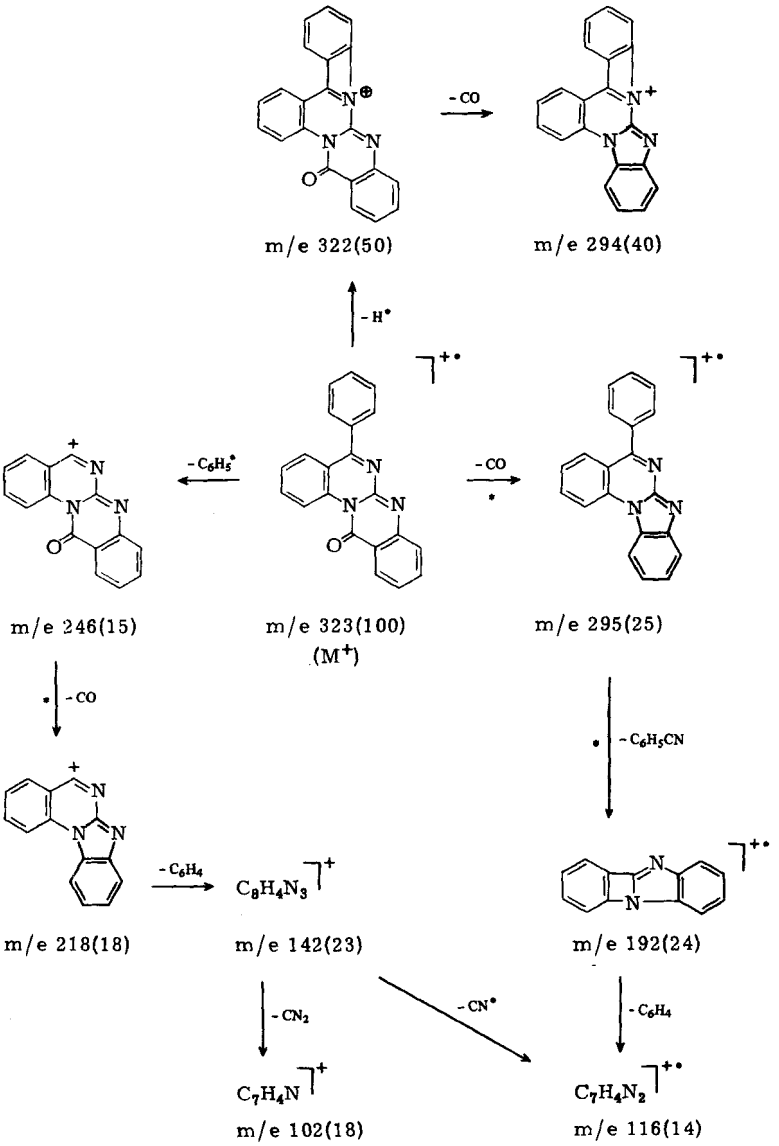
The molecular ion m/e 323 (M^+) is the base peak and fragments to give ion m/e 322 by the loss of hydrogen radical (proximity effect)[8], which in turn loses carbon monoxide to give ion m/e 294. The loss of carbon monoxide from the molecular ion is also observed to afford ion m/e 295 which by the loss of phenyl cyanide gives ion m/e 192. These losses are substantiated by the presence of corresponding metastable peaks. Ion m/e 294 may also arise by the loss of hydrogen radical from ion m/e 295. Molecular ion further fragments by the loss of phenyl radical to furnish ion m/e 246, which on subsequent loss of carbon monoxide affords ion m/e 218. Further fragmentation takes place as illustrated in scheme 1.

Compounds **4b–e** having one and two chlorine atoms also fragment in a similar manner.

Biological Evaluation

Some representative members of the series were tested for their analgesic and antiinflammatory actions in rats according to the literature methods[9,10]. They exhibited mild to moderate antiinflammatory activity and were non-toxic upto a dose level of 300 mg/kg p.o. No gross central or autonomous nervous system effects were noted. It was

Schema 1



observed that the introduction of chlorine enhances antiinflammatory activity to a considerable extent as seen by the results summarized in table 2.

These compounds have also been tested for their antimicrobial activity using the disc method against *B.subtilis, E.coli, S.aureus, A.flavus, P.tardum, H.halodes* and *F. oxysporium*. None of the test compounds showed any appreciable activity.

Table 1: *5-Aryl-12H-quinazolino[3,2-a]quinazolin-12-ones* **4**

4	X	X^1	R	R^1	R^2	Yield (%)	m.p. (°C)	Molecular formula*	I.R. (KBr) (cm^{-1})
a	H	H	H	H	H	68	234–236	$C_{21}H_{13}N_3O$ (323.4)	1685, 1590
b	H	H	H	Cl	H	76	257–258	$C_{21}H_{12}ClN_3O$ (377.8)	1680, 1585
c	H	H	Cl	H	Cl	78	264	$C_{21}H_{11}Cl_2N_3O$ (412.2)	1680, 1585
d	Cl	H	H	H	H	82	280–281	$C_{21}H_{12}ClN_3O$ (377.8)	1685, 1595
e	Cl	H	H	Cl	H	75	258–259	$C_{21}H_{11}Cl_2N_3O$ (412.2)	1690, 1595
f	Cl	H	Cl	H	Cl	68	261–262	$C_{21}H_{10}Cl_3N_3O$ (446.6)	1685, 1590
g	Cl	Cl	H	H	H	75	243–244	$C_{21}H_{11}Cl_2N_3O$ (412.2)	1685, 1585
h	Cl	Cl	H	Cl	H	62	256	$C_{21}H_{10}Cl_3N_3O$ (446.6)	1680, 1585
i	Cl	Cl	Cl	H	Cl	65	222–225	$C_{21}H_9Cl_4N_3O$ (481.0)	1685, 1595

* The elementary analyses were in satisfactory agreement with the calculated values

Tables 2: *Analgesic and Antiinflammatory Activity*

Compounds	Dose (mg/kg)	% protection of pain (Tail Clip)	% inhibition of inflammation	
			Carrageenin	Cotton pellet
4a	200	–	–	12.4
4d	200	26.7	14.8	–
4e	100	15.8	13.2	–
4f	100	–	17.5	10.2
4g	100	–	24.8	21.4
4i	100	22.5	28.0	25.7

Experimental Part

MP: Boetus heating table apparatus, uncorr. *IR spectra*: Perkin Elmer 221 spectrophotometer. *Mass spectra*: Jeol D.300 at 70 eV.

2-Chloro-4-arylquinazolines[11] **2**

General Procedure: To 10 g 4-aryl-2(1H)-quinazolinone (**1**) was added 40 ml phosphorus oxychloride and refluxed at 120–130° for 40 min. After distilling off about 20 ml of phosphorus oxychloride the reaction mixture was poured into crushed ice. It was neutralized with aqueous sodium carbonate and the crude product obtained was recrystallized from ethanol.

5-Aryl-12H-quinazolino[3,2-a]quinazolin-12-ones **4**

General Procedure: A mixture of **2** and the anthranilic acid **3** were taken in equimolar quantities and heated in an oil bath at 160–170° for 90 min. After the completion of heating, the brittle mass obtained was powdered well and washed with sodium hydrogen carbonate solution (10 %). It was recrystallized from ethanol/methanol to get the pure compound **4**. The compounds prepared are listed in table 1.

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