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Tricyclic Amides: A New Class of Systemic Fungicides Active against Rice Blast Disease

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The preparation of several pyrrolo[3,2,1-*ij*]- and pyrido[3,2,1-*ij*]quinoline derivatives and their activity against rice blast disease are described. Although a wide range of substitution is permitted within these classes, highest activity is displayed by the simplest amide members, particularly 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (**20**, 4-lilolidone), which shows excellent protectant activity in greenhouse evaluation at concentrations of 5–10 ppm.

Rice blast disease (RBD), caused by *Piricularia oryzae*, is one of the major fungal diseases of crop plants in the world and the most important diseases of rice (Ou and Jennings, 1969). A number of fungicides for its control have been developed, including copper salts, the antibiotics blasticidin S and kasugamycin, organophosphates (Hinosan and Kitazin), and pentachlorobenzyl alcohol (Blastin). Despite extensive control measures, however, it remains widely prevalent and troublesome. In recent years, there has been a particularly strong interest in discovering systemic fungicides for its control, since these would require less frequent application than the traditional locally acting foliar protectants.

In the course of screening selected compounds representing a variety of structures, we discovered that the tricyclic amide 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]-quinolin-2-one (compound **3** in Table I) protects rice plants against experimental RBD in the greenhouse. While this compound ("2-lilolidone") had been described in the literature by Kato et al. (1971), we have found no previous reference to fungicidal activity associated with it or closely related structures; it might conceivably be distantly related to the systemic carboxanilide fungicides, even though the latter controls a different spectrum of fungal diseases (Snel et al., 1970). Its activity was particularly surpising because in vitro, this compound showed little or no activity against *P. oryzae*. Greenhouse studies revealed that **3** applied to the floodwater of rice plants is *systemically* active against RBD and well tolerated by the plants, and these findings led to the preparation and testing of the pyrrolo[3,2,1-*ij*]- and pyrido[3,2,1-*ij*]quinolones described herein, with the aim of optimizing activity in this promising new class of fungicides.

Pfizer Central Research, Sandwich, Kent, United Kingdom, and Pfizer Central Research, Pfizer Inc., Groton, Connecticut.

CHEMICAL SYNTHESIS

The primary tricyclic ring structures listed in Tables I and II were generally synthesized either from tetrahydroquinoline (THQ) or from indoline (I) by N-acylation with the appropriate reagent (ω-chloroacyl chloride, diester, etc.), followed by ring closure [in the presence of aluminum chloride, polyphosphoric acid, etc. (Scheme I)]. Substituted derivatives of these systems were synthesized either from the appropriately substituted THQ or I or by chemical derivatization as indicated in Tables I and II. References relating to the exact synthetic procedure are given in Tables I and II, apart from the following, hithero undescribed in the literature.

Decahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (19). Compound **3** (5.4g) was hydrogenated (room temperature; 50 psi) over platinum oxide (0.2 g) in glacial acetic acid (170 mL) in a Parr apparatus for 6 h. More platinum oxide was then added and hydrogenation continued for another 2 h. The catalyst was separated and the solution evaporated. Water was added to the residue and the whole extracted with ether (2 × 100 mL). The ether layer was washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Evaporation afforded an oil which solidified after drying in vacuo. Recrystallization from hexane afforded a solid (1.8 g) of mp 49–50 °C, *m/e* 179, assumed to be a mixture of isomers. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.6; N, 7.8. Found: C, 73.6; H, 9.6; N, 7.8.

Decahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (25) was prepared in a similar manner from 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (**20**) as an oil, *m/e*

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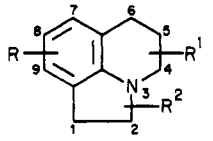
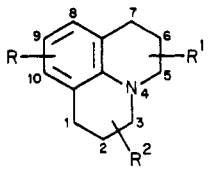
Table I. Pyrrolo[3,2,1-*ij*]quinolines: Protectant Activity against *P. oryzae* in the Greenhouse[a]



no.	R	R¹	R²	% inhibition at treatment level, ppm 100	10	5	synthetic starting material[b]	method of preparation[c]	ref[f]
1	H	H	H	56	22	22	20	LAH reduction	A
2	H	6-oxo	H	55	0	0	I	(1) CH_2=CHCN; (2) KOH; (3) PPA	B
3	H	H	2-oxo	100	99	61	THQ	(1) $ClCH_2COCl$; (2) $AlCl_3$	C
4	H	H	2-thioxo	57	41	0	3	P_2S_5	C
5	8-Me	H	2-oxo	99	43	20	6-Me-THQ	(1) $ClCH_2COCl$; (2) $AlCl_3$	C
6	8-Bu^t	H	2-oxo	99	71	45	3	$Bu^tCl/AlCl_3$	C
7[d]	8-OH	H	2-oxo	54	35	15	6-MeO-THQ	(1) $ClCH_2COCl$; (2) $AlCl_3$	C
8	8-Cl	H	2-oxo	72	39	0	16	Zn	C
9	8-Br	H	2-oxo	87	39	36	3	Br_2	C
10	8-HCO	H	2-oxo	58	31	0	3	$DMF/POCl_3$	C
11	8-MeCO	H	2-oxo	53	39	0	3	CH_3CO_2H/PPA	C
12	8-PhCO	H	2-oxo	94	26	27	3	$PhCO_2H$/PPA	C
13	H	4-Me	2-oxo	55	41	22	2-Me-THQ	(1) $ClCH_2COCl$; (2) $AlCl_3$	C
14	H	H	1-Ph-2-oxo	37	0	0	THQ	(1) $PhClCHCOCl$; (2) $AlCl_3$	D
15	H	H	1-Me-2-oxo	96	59	20	THQ	(1) $CH_3ClCHCOCl$; (2) $AlCl_3$	D
16	8-Cl	H	1,1-$(Cl)_2$-2-oxo	68	25	27	3	Cl_2	C
17	8-Cl	H	1,1-$(Ph)_2$-2-oxo	30	39	10	16	$C_6H_6/AlCl_3$	C
18	8-Cl	H	1,2-dioxo	38	35	0	16	50% aq MeOH/CH_3CO_2Na	C
19	3a,6a,7,8,9,9a-hexahydro	H	2-oxo	0	0	0	3	Pt/H_2	E
20	H	4-oxo	H	100	99	88	I	(1) $ClCH_2COCl$; (2) $AlCl_3$	E
21	H	4-thioxo	H	100	84	67	20	P_2S_5	C
22	8-Br	4-oxo	H	98	72	37	20	Br_2	C
23	8-CN	4-oxo	H	37	0	0	20	CuCN	C
24	8-MeCO	4-oxo	H	92	25	18	20	CH_3CO_2H/PPA	C
25	3a,6a,7,8,9,9a-hexahydro	4-oxo	H	0	0	0	20	Pt/H_2	E
26[e]	H	4-oxo-Δ^5	H	99	59	22	I	(1) PhCH=CHCOCl; (2) $AlCl_3$	E
27	H	6-Ph-4-oxo-Δ^5	H	49	8	0	I	(1) $PhCOCH_2CO_2Et$; (2) PPA	C

[a] For full testing details, see Biological Evaluation. [b] I = indoline; THQ = tetrahydroquinoline; compound numbers refer to column 1, this table. [c] LAH = lithium aluminum hydride; PPA = polyphosphoric acid. [d] Demethylation occurs during the cyclization. [e] Dephenylation occurs during cyclization; see Chemical Synthesis. [f] Method A: Hallas and Taylor (1964). Method B: Rapoport and Tretter (1958). Method C: Bass et al. (1975). Method D: Kato et al. (1971). Method E: see Chemical Synthesis, this paper.

Table II. Pyrido[3,2,1-*ij*]quinolines: Protectant Activity against *P. oryzae* in the Greenhouse[a]



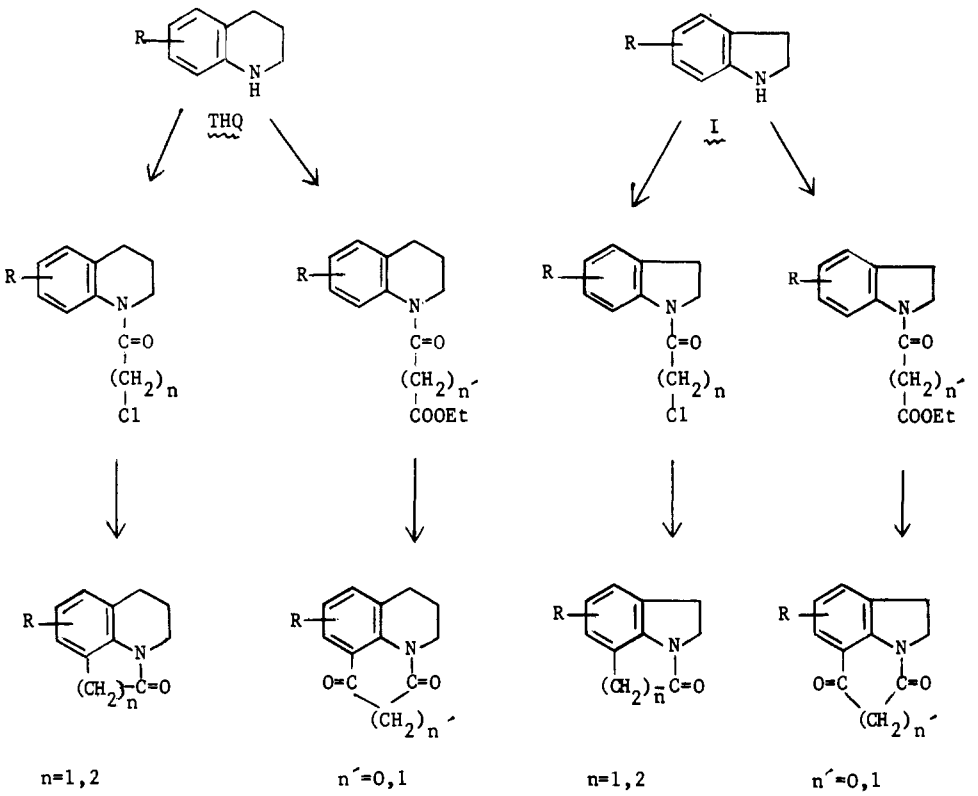
no.	R	R¹	R²	% inhibition at treatment level, ppm 100	10	5	synthetic starting material[b]	method of preparation[c]	ref
28	H	H	3-oxo	99	64	65	THQ	(1) $ClCH_2CH_2COCl$; (2) $AlCl_3$	G
29	H	H	3-thioxo	100	87	70	28	P_2S_5	C
30	9-Me	H	3-oxo	79	32	14	6-Me-THQ	(1) $ClCH_2COCl$; (2) $AlCl_3$	C
31[d]	9-MeCOO	H	3-oxo	56	29	26	6-MeO-THQ	(1) $ClCH_2CH_2COCl$; (2) $AlCl_3$; (3) Ac_2O	C
32[e]	H	H	Δ^1-3-oxo	96	58	29	THQ	(1) PhCH=CHCOCl; (2) $AlCl_3$	E
33	9-Me	H	Δ^1-1-Me-3-oxo	31	20	0	6-Me-THQ	(1) $CH_3COCH_2CO_2Et$; (2) H_2SO_4	C
34	9-MeO	H	Δ^1-1-Me-3-oxo	30	0	0	6-MeO-THQ	(1) $CH_3COCH_2CO_2Et$; (2) H_2SO_4	C
35	H	H	2-Ph-1,3-dioxo	80	64	0	THQ	$PhCH(CO_2Et)_2$	C
36	H	H	2-Pr^n-1,3-dioxo	61	0	0	THQ	$PrCH(CO_2Et)_2$	C

[a] See Biological Evaluation for full details of testing. [b] THQ = tetrahydroquinoline. [c] Method G: Yu (1951); methods C and E as described in Table I. [d] Demethylation occurs during the $AlCl_3$ cyclization. [e] Dephenylation occurs during cyclization; see Chemical Synthesis.

179, again assumed to be a mixture of isomers. Anal. Calcd for $C_{11}H_{17}NO$: N, 7.8. Found: N, 7.8.

1,2,5,6-Tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (20). A solution of indoline (320 g, 2.68 M) in dry

Scheme I. General Synthetic Routes



acetone (1.32 L) was cooled in an ice bath. 3-Chloropropionyl chloride (358 g, 2.815 M) was slowly added, with stirring, at such a rate to keep the reaction temperature below 50 °C. After addition was complete (35 min), the mixture was heated under reflux for 2 h and cooled. It was then poured into aqueous hydrochloric acid (10%, 3.4 L) with stirring and cooling. The solid that formed was granulated at 15 °C, filtered, washed with water, and dried at 40 °C. This yielded 458 g (81%) of the *N*-(3-chloropropionyl)indoline.

A solution of the *N*-(3-chloropropionyl)indoline (72 g, 0.345 M) in cyclohexane (240 mL) containing aqueous hydrobromic acid (7.2 mL, 60% w/w) was treated continuously with stirring at 50 °C, with powdered anhydrous aluminum chloride (158.4 g, 1.187 M), added portionwise. After completion of the addition, the reaction mixture was heated under reflux, with stirring, for 24 h. After the mixture was cooled to 30 °C, a further lot of aluminum chloride (45.9 g) and aqueous hydrobromic acid (2.16 mL) was added and the whole stirred under reflux for a further 24 h. The mixture was cooled to 40 °C and poured onto a mixture of ice and concentrated hydrochloric acid (360 mL). The reaction flask was washed with toluene (2 × 330 mL). These washings were added to the bulk, and then the mixture stirred for 10 min, after which the organic layer was separated, washed with water (1.2 L), and dried ($MgSO_4$). Evaporation gave a solid which was crystallized from cyclohexane, affording the quinolin-4-one (**20**, 37 g, 62%) as material of mp 112–113 °C [lit. mp 112–113 °C (Hallas and Taylor, 1964)].

1,2-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (26). Cinnamoyl chloride (16.6 g, 0.1 M) was added dropwise to indoline (12.9 g, 0.11 M) in toluene (150 mL) in the presence of triethylamine (13.85 g, 0.1 M). The mixture was refluxed for 3h, cooled, filtered, and poured into water, and the organic layer washed with diluted NaOH and diluted HCl. The toluene layer was then dried ($MgSO_4$) and evaporated to dryness. The product, *N*-cinnamoylindoline, was crystallized from petroleum ether 60/80 as a solid, mp 117–118 °C (8.0 g, 30%). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.9; H, 6.1, N, 5.6. Found: C, 82.0, H, 6.5, N, 5.5.

A mixture of *N*-cinnamoylindoline (2.0 g, 0.008 M) and aluminum chloride (3.2 g, 0.024 M) was heated gently on an oil bath until a homogeneous melt was produced, and heating was discontinued to allow the initial exothermic reaction to subside. The product was then heated for a further 90 min at 115 °C. After being cooled, the mixture was treated with cracked ice, partitioned into chloroform, washed 3 times with 10% sodium carbonate solution, dried ($MgSO_4$), and evaporated to give a pale pink solid which crystallized from benzene as pink cubes, mp 157–158 °C [lit. mp 157–158 °C, using a different method of preparation (Brooker and Heseltine, 1954)] (1.0 g, 70%), of 1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one. That dephenylation had occurred during cyclization was shown by the absence of characteristic aromatic proton signals in the NMR and the chemical analysis. Anal. Calcd for $C_{11}H_9NO$: C, 77.3; H, 5.3; N, 8.2. Found: C, 77.6; H, 5.4; N, 8.0. A similar dephenylation reaction has been reported by Neidlein and Sequil-Camargo (1979).

6,7-Dihydro-3*H*,5*H*-pyrido[3,2,1-*ij*]quinolin-3-one (32) was formed similarly from *N*-cinnamoyl-1,2,3,4-tetrahydroquinoline [prepared by the method of Schuyler et al. (1966)] in 6% yield, mp 98–99 °C [lit. mp 102–103 °C, using a different method of preparation (Brooker and Heseltine, 1954)].

BIOLOGICAL EVALUATION

Biological screening for activity against RBD was carried out at the Crop Protection Institute, Durham, NH, under the direction of Dr. Robert J. Norton.

Evaluation of Protectant Activity. Compounds were formulated as 10% acetone emulsions (0.2% Span 85; 0.05% Tween 80; 99.75% acetone) in deionized water and evaluated at 100, 10, and 5 ppm of active ingredient.

Approximately 150 mL of test solution was uniformly sprayed at 40 lb of pressure for 60 s onto rice plants (*Oryza sativa*) in the fully developed second-leaf growth stage (with the fourth leaf fully expanded). After being dried, treated plants were spray-inoculated at 30 lb of pressure with an aqueous spore suspension of *P. oryzae* and then immediately placed in an incubation chamber maintained at 70–80 °F and 95% relative humidity. After 18–24 h, plants were removed to the greenhouse for disease development. Infection lesions were sufficiently developed within 5 days after inoculation to permit assessment of the control. Disease severity was determined by an actual count of the number of infection lesions developed on untreated inoculated controls. Effectiveness of treatment, expressed as a percentage, was determined by direct comparison of the number of infection lesions appearing on the respective treated plants compared directly with those lesions appearing on untreated inoculated controls. Phenylmercuric acetate was used as a reference standard at a concentration of 200 ppm, at which level it was found to be 100% effective. All units of test included a minimum of three replicates.

Testing of Compound 3 in Vitro. Compound **3** was applied in acetone to absorbent paper disks (No. 750-E, Schleicher & Schuell Co., Keene, NH) at the rates of 250, 500, 750, and 1000 mg/disk. The acetone was evaporated and the disks were transferred to whole wheat agar (WWA) seeded with *P. oryzae*. After 1 week at room temperature, no zones of inhibition were observed around the disks treated with the four concentrations of **3**.

RESULTS AND DISCUSSION

From the results quoted in Tables I and II, it can be seen that several compounds displayed high protectant activity against rice blast disease, particularly at 100 ppm, in both the pyrrolo[3,2,1-*ij*]- and pyrido[3,2,1-*ij*]quinolinone series. However, it was clear that activity was considerably reduced in the absence of a carbonyl function adjacent to the bridgehead nitrogen (**1** and **2**), and activity was lost when the aromatic ring was reduced (**19** and **25**). Activity was retained when the carbonyl function was replaced with a thiocarbonyl function (cf. **3** and **4**, **20** and **21**, and **28** and **29**). Some activity was retained in the presence of two carbonyl functions in the ring (**18**, **35**, and **36**) and substitution as well as unsaturation of the nonaromatic rings was permitted (**13**, **14**, **15**, **16**, **17**, **26**, **27**, **32**, **33**, and **34**). Substitution of the aromatic ring was allowed by alkyl (**5**, **6**, **30**, and **33**), hydroxy (**7**), alkoxy (**34**), halogen (**8**, **9**, **16**, **17**, **18**, and **22**), cyano (**23**), formyl (**10**), acyl (**11**, **12**, and **24**), and acyloxy groups (**31**). However, the highest protectant activity at lowest spray concentrations was displayed by the simplest members of the series, particularly **3** and **20**, 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (2-lilolidone) and 1,2,5,6-tetrahydro-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-4-one (4-lilolidone), respectively.

CONCLUSIONS AND REMARKS

Compounds **3** and **20** were taken into extensive secondary evaluation in the greenhouse, and it was established that the potency of **20** was approximately double that of **3**. Full details of greenhouse and field evaluations for **20** (1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one, 4-lilolidone) will be reported elsewhere. [Compound **20** is undergoing extensive development by Ciba-Geigy Ltd. as CGA 49104, for which "pyroguilon" is also an ISO common name proposal; preliminary results have been reported by Schwinn et al. (1979).]

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