# Synthesis and Antiallergic Activity of Some Acidic Derivatives of 4*H*-Pyrimido[2,1-*b*]benzazol-4-ones

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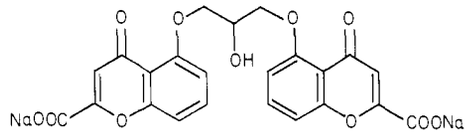
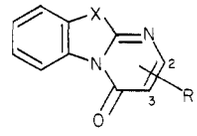
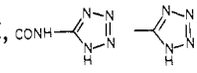
Reactions of 2-aminobenzothiazole, 2-aminobenzoxazole, and 2-amino-1-methylbenzimidazole with dimethyl aminofumarate (DMAF) or diethyl ethoxymethylenemalonate (DEEM) led to 2- or 3-carboxy-4*H*-pyrimido[2,1-*b*]benzazol-4-ones, respectively. Subsequent derivatization of these carboxylic acids gave the corresponding tetrazolylcarboxamides and tetrazoles. These acidic compounds were tested in the rat passive cutaneous anaphylaxis (PCA) assay as potential antiallergic agents. Many of the compounds displayed activity comparable to that shown by disodium cromoglycate (DSCG) when tested by the intraperitoneal route, and some, unlike DSCG, also showed activity when tested orally.

Disodium cromoglycate (DSCG, 1) has been shown to



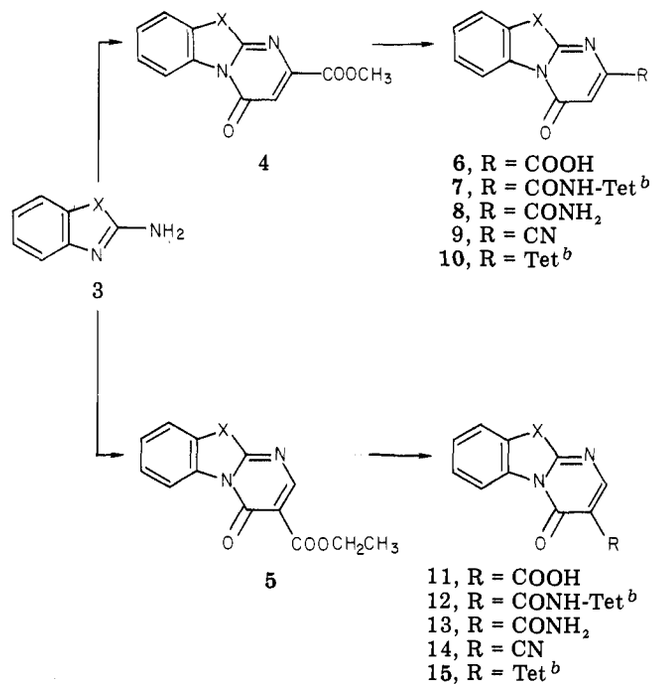
1 (DSCG)



2, X = O, S, $NCH_3$;
R = COOH, 

be useful for the prophylatic treatment of the allergic disease state.[1] The passive cutaneous anaphylaxis (PCA) model in rats provides a convenient method for measuring the potential antiallergic activity of compounds that may act like DSCG.[2] For these reasons, there has been considerable effort in many laboratories to discover additional DSCG-like antiallergic agents.[3] Based on earlier antiallergic research conducted in our laboratories,[4] as well as work reported by others,[5] we felt that the incorporation of an acidic functionality [carboxylic acid, *N*-(1*H*-tetrazol-5-yl)carboxamide, or tetrazole] at either the 2- or 3-position of the 4*H*-pyrimido[2,1-*b*]benzazol-4-one ring system (**2**, X = S, O, $NCH_3$) might result in compounds of antiallergic interest; therefore, we began a systematic study of these compounds. Recent reports from other laboratories, which disclose the antiallergic activity of several such compounds,[6] prompted this report of our own work.

Scheme I[a]



4

6, R = COOH
7, R = CONH-Tet[b]
8, R = $CONH_2$
9, R = CN
10, R = Tet[b]

3

5

11, R = COOH
12, R = CONH-Tet[b]
13, R = $CONH_2$
14, R = CN
15, R = Tet[b]

[a] a, X = S; b, X = O; c, X = $NCH_3$. [b] Tet = tetrazol-5-yl = 

**Chemistry.** With some exceptions, the *N*-(1*H*-tetrazol-5-yl)carboxamides and the tetrazolyl compounds were prepared from the corresponding carboxylic acids. The acids were prepared from the requisite 2-aminobenzazoles as described in our earlier report[7] and as illustrated in Scheme I. Thus, reaction of the 2-aminobenzazole **3** with dimethyl aminofumarate (DMAF) and subsequent saponification gave the 2-carboxylic acids **6**. In complementary fashion, reaction of an amine **3** with diethyl ethoxymethylenemalonate (DEEM) and subsequent thermal cyclization and hydrolysis gave the 3-carboxylic acid **11**.[7,8] The *N*-(1*H*-tetrazol-5-yl)carboxamides **7** and **12** were prepared from these acids by treatment first with thionyl chloride, to form the corresponding acyl chloride, and then with 5-aminotetrazole. The tetrazolyl derivatives **10** and **15** were generally prepared by conversion of the requisite

(1) J. S. G. Cox, J. E. Beach, A. M. J. N. Blair, A. J. Clarke, J. King, T. B. Lee, D. E. E. Loveday, G. F. Moss, T. S. C. Orr, J. T. Ritchie, and P. Sheard, *Adv. Drug. Res.*, **5**, 115 (1970).
(2) J. Goose and A. M. J. N. Blair, *Immunology*, **16**, 749 (1969).
(3) (a) J. P. Devlin, *Annu. Rep. Med. Chem.*, **16**, 61 (1981). (b) D. L. Temple, Ed., "Drugs Affecting the Respiratory System", American Chemical Society, Washington, DC, 1980.
(4) (a) E. H. Erickson, L. R. Lappi, T. K. Rice, K. F. Swingle, and M. Van Winkle, *J. Med. Chem.*, **21**, 984 (1978). (b) J. J. Wade, E. H. Erickson, R. F. Hegel, L. R. Lappi, and T. K. Rice, *ibid.*, **21**, 941 (1978). (c) E. H. Erickson, C. F. Hainline, L. S. Lenon, C. J. Matson, T. K. Rice, K. F. Swingle, and M. Van Winkle, *ibid.*, **22**, 816 (1979).
(5) G. P. Ellis, G. J. P. Becket, D. Shaw, H. K. Wilson, C. J. Vardey, and I. F. Skidmore, *ibid.*, **21**, 1120 (1978).
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(8) (a) D. W. Dunwell and D. Evans, *J. Chem. Soc. C*, 2094 (1971). (b) H. Ogura, M. Kawano, and T. Itoh, *Chem. Pharm. Bull.* **21**, 2019 (1973). (c) R. J. Alaimo, *J. Heterocycl. Chem.*, **10**, 769 (1973).

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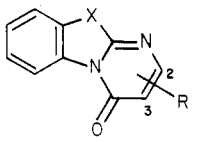
Table I. Acidic Derivatives of 4*H*-Pyrimido[2,1-*b*]benzazol-4-ones



| no. | X | R | formula[a] | mp, °C | yield, % | MED,[b] mg/kg ip | MED,[b] mg/kg po |
|---|---|---|---|---|---|---|---|
| 6a | S | 2-COOH | $C_{11}H_6N_2O_3S$ | 271–272 dec | 49 | >5 | >10 |
| 6b | O | 2-COOH | $C_{11}H_6N_2O_4$ | 280–281 dec | 65 | 5 | >10 |
| 6c | $NCH_3$ | 2-COOH | $C_{12}H_9N_3O_3 \cdot H_2O$ | 274–275 dec | 78 | >5 | >10 |
| 7a | S | 2-CONHCHN$_4$ | $C_{12}H_7N_7O_2S$[c] | >300 | 61 | 1.25 | >10 |
| 7b | O | 2-CONHCHN$_4$ | $C_{12}H_7N_7O_3$ | 315–320 | 14 | 1.25 | >10 |
| 7c | $NCH_3$ | 2-CONHCHN$_4$ | $C_{13}H_{10}N_8O_2$ | 315–317 | 6 | 1.25 | 10 |
| 10a | S | 2-CHN$_4$ | $C_{11}H_6N_6OS$ | >300 | 79 | 5 | >10 |
| 10b | O | 2-CHN$_4$ | $C_{11}H_6N_6O_2$ | 305–307 | 42 | 1.25 | >10 |
| 10c | $NCH_3$ | 2-CHN$_4$ | $C_{12}H_9N_7O$ | 302–304 | 76 | 5 | |
| 11a | S | 3-COOH | $C_{11}H_6N_2O_3S$ | 230–232 dec | 61 | >5 | >10 |
| 11b | O | 3-COOH | $C_{11}H_6N_2O_4$ | 268–270 dec | 32 | >5 | >10 |
| 11c | $NCH_3$ | 3-COOH | $C_{12}H_9N_3O_3$ | 345–348 dec | 93 | 0.63[d] | >10 |
| 12a | S | 3-CONHCHN$_4$ | $C_{12}H_7N_7O_2S$ | >300 | 85 | 1.25 | >10 |
| 12b | O | 3-CONHCHN$_4$ | $C_{12}H_7N_7O_3$ | 326–328 | 83 | 1.25 | 10 |
| 12c | $NCH_3$ | 3-CONHCHN$_4$ | $C_{13}H_{10}N_8O_2$ | >300 | 57 | 0.31 | >10 |
| 15a | S | 3-CHN$_4$ | $C_{11}H_6N_6OS$ | >300 | 36 | 1.25 | >10 |
| 15b | O | 3-CHN$_4$ | $C_{11}H_6N_6O_2$ | >300 | 37 | 1.25 | 5 |
| 15c | $NCH_3$ | 3-CHN$_4$ | $C_{12}H_9N_7O$ | >300 | 42 | 0.31 | 2.5 |

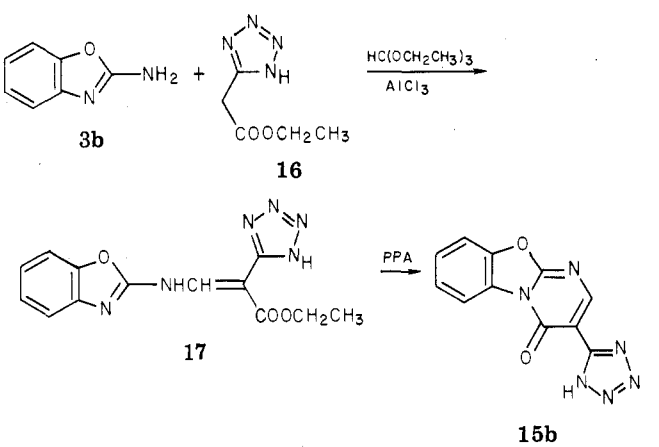
[a] The results of C, H, and N analyses are within ±0.4% of the theoretical values except as noted. [b] See Biological Methods section of the text for a definition of MED. [c] C: calcd, 46.0; found, 45.5. [d] Tested at 10, 2.5, and 0.63 mg/kg ip.

esters ($NH_3$/ethanol) or acids ($SOCl_2$, then $NH_3$) to the amides **8** and **13**, dehydration of these amides to the nitriles **9** and **14** ($PCl_5$/DMF), and reaction of these nitriles with sodium azide and ammonium chloride in DMF.

The 3-substituted benzoxazoles **11b** and **15b** proved to be special cases. We have already reported that attempted saponification of the ester **5b** gives a ring-opened product rather than the desired acid and that we resorted to a LiI/pyridine cleavage of the corresponding methyl ester (derived from dimethyl ethoxymethylenemalonate) in order to obtain acid **11b**.[7] This acid could be readily converted to the amide **13b** and the nitrile **14b**, but a similar ring-opened product, rather than tetrazole formation, was observed upon reaction of **14b** with sodium azide and ammonium chloride. Several alternative approaches to this tetrazole were unfruitful, including attempts to prepare the tetrazole moiety before cyclization to the tricycle, as well as attempts to make and use an imidoyl chloride rather than the nitrile.[9] A useful procedure was finally realized and is illustrated in Scheme II. Thus 2-aminobenzoxazole, triethyl orthoformate, and the readily available ethyl tetrazol-5-ylacetate **16**[10] were briefly heated together with a small amount of aluminum trichloride to give the adduct **17**. Cyclization could not be effected thermally, but heating in polyphosphoric acid gave the desired tricyclic **15b**. This procedure may be a short, convenient method for preparing tetrazolylpyrimidines and tetrazolylquinolines, and its optimization and generalization are currently under study in our laboratory.

**Biological Methods.** The acids, tetrazolylcarboxamides, and tetrazoles were tested for their ability to inhibit the PCA reaction in Sprague–Dawley rats by the method previously described.[4] Initial testing was done by ip injection of a Klucel suspension of the compounds at doses of 5, 1.25, and/or 0.31 mg/kg, with six animals at each dose level. The lowest such dose that displayed greater than 50% inhibition with $p \leq 0.05$ (Student's $t$ test) is recorded in Table I as the minimum effective dose (MED ip). For DSCG, sufficient information was obtained to determine an $ID_{50}$ value; this value, along with its 95% confidence range, is 2.6 (1.9–3.3) mg/kg ip, based on 44 experiments with six animals each. Some of our compounds were then similarly tested by oral dosing, again as a Klucel suspension, at 10, 5, and/or 2.5 mg/kg, and a similarly derived MED po is reported for these compounds. DSCG is ineffective by the oral route, but doxantrazole, a reference agent that has received some clinical study,[11] has an oral MED of 5 mg/kg in our rat PCA assay.

Scheme II




## Results and Discussion

Table I shows the PCA results for the acidic derivatives of the 4*H*-pyrimido[2,1-*b*]benzazol-4-ones. All 12 of the compounds with a tetrazole or tetrazolylcarboxamide function as the acidic substituent were active at ip doses ≤5 mg/kg; only two of the six carboxy-substituted compounds displayed such potency. Furthermore, compounds with the acidic function in the 3-position, rather than the

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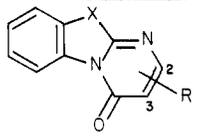
(10) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).
(11) J. F. Batchelor, M. J. Follenfant, L. G. Garland, J. H. Gorvin, A. F. Green, H. F. Hodson, D. T. D. Hughes, and J. E. Tateson, *Lancet. 1*, 1169 (1975).

Table II. Carboxamide and Carbonitrile Derivatives of 4*H*-Pyrimido[2,1-*b*]benzazol-4-ones



| no. | X | R | formula[a] | mp, °C | yield, % | method |
|---|---|---|---|---|---|---|
| 8a | S | 2-$CONH_2$ | $C_{11}H_7N_3O_2S$ | >300 | 96 | B |
| 8b | O | 2-$CONH_2$ | $C_{11}H_7N_3O_3$ | 296–298 | 75 | B |
| 8c | $NCH_3$ | 2-$CONH_2$ | $C_{12}H_{10}N_4O_2$ | 328–330 | 51 | C |
| 9a | S | 2-CN | $C_{11}H_5N_3OS$ | 190–192 | 93 | D |
| 9b | O | 2-CN | $C_{11}H_5N_3O_2$ | 178–180 | 50 | D |
| 9c | $NCH_3$ | 2-CN | $C_{12}H_8N_4O$ | 206–208 | 87 | D |
| 13a | S | 3-$CONH_2$ | $C_{11}H_7N_3O_2S$ | >300 | 73 | C |
| 13b | O | 3-$CONH_2$ | $C_{11}H_7N_3O_3$ | 286–287 | 91 | C |
| 13c | $NCH_3$ | 3-$CONH_2$ | $C_{12}H_{10}N_4O_2$ | 293–295 | 67 | C |
| 14a | S | 3-CN | $C_{11}H_5N_3O_3$ | 264–266 | 85 | D |
| 14b | O | 3-CN | $C_{11}H_5N_3O_2$ | 241–243 | 81 | D |
| 14c | $NCH_3$ | 3-CN | $C_{12}H_8N_4O$ | 293–295 | 90 | D |

[a] The compounds were generally used in subsequent reactions without elemental analysis. Their identity was indicated by spectral data, as well as by spectral and microanalytical data of subsequent reaction products.

2-position, were generally more potent. For compounds substituted in the 2-position, the tetrazolylcarboxamide function seems to have a slight advantage over the tetrazole function when tested ip; no such advantage is observed in the present study for compounds substituted in the 3-position. Finally, it should be noted that the two compounds most active by the ip route, **12c** and **15c**, are both benzimidazole derivatives, and both have the acidic function in the 3-position of the pyrimidine ring. These two compounds have MED values of 0.31 mg/kg ip and are, thus, approximately eightfold more potent than DSCG in our PCA assay.

PCA testing by the oral route uncovered four compounds with activity at doses ≤10 mg/kg. For compounds substituted in the 3-position, the tetrazole function may have some advantage over the tetrazolylcarboxamide function. The two most potent compounds, **15b** (MED = 5 mg/kg po) and **15c** (MED = 2.5 mg/kg po), are compounds with a tetrazole substituent in the 3-position.

In summary, the work reported here indicates that some acidic derivatives of the 4*H*-pyrimido[2,1-*b*]benzazol-4-one ring system have ip PCA inhibitory activity in the rat comparable to or somewhat greater than that of DSCG and oral PCA inhibitory activity in the rat comparable to that of doxantrazole.[12] The compounds described here may therefore be useful in the treatment of allergic diseases. Further study of substituted analogues of these compounds, particularly of the benzimidazole-derived compounds **12c** and **15c**, may lead to compounds with increased potency.

## Experimental Section

The melting points were obtained with a Mel-Temp block or a Uni-melt apparatus and are uncorrected. IR spectra were obtained, using Nujol mulls, with a Perkin-Elmer infracord spectrophotometer; $^1H$ NMR spectra were measured with a Varian T-60 or a Varian XL-100 spectrometer. The spectral data are consistent with the assigned structures in all cases. Elemental analyses were determined by J. H. Gagnon and his co-workers in the Central Research Analytical Group, 3M Co., and the results, except where noted, are within ±0.4% of the theoretical values.

The esters **4** and **5** and the carboxylic acids **6** and **11** (Table I) were prepared as reported previously.[7] The tetrazolylcarboxamides **7** and **12** were prepared by general method A. The tetrazole derivatives **10**, **15a**, and **15c** were prepared by sequential application of general methods B, D, and E, or C, D, and E.

***N*-Tetrazol-5-ylcarboxamides (7 and 12). General Method A. Table I.** The appropriate carboxylic acid (**6** or **11**; 10 mmol) was refluxed for 3 h in 100 mL of thionyl chloride. The solvent was removed in vacuo, and the last traces of thionyl chloride were eliminated by suspending the residue three times in 75 mL of anhydrous benzene and concentrating in vacuo. The residue was suspended in 75 mL of anhydrous diglyme, and the mixture was heated to 100 °C and then treated with anhydrous 5-aminotetrazole (2.55 g, 30.0 mmol). After stirring for 1 h at 100 °C, the mixture was cooled, and the solid was collected by filtration. The product was purified by thoroughly washing first with hot (80–100 °C) DMF and then with hot water.

**4-Oxo-4*H*-pyrimido[2,1-*b*]benzazolecarboxamides (8a and 8b). General Method B. Table II.** The ester (**4a** or **4b**; 20 mmol) was stirred overnight at room temperature in 250 mL of saturated ethanolic ammonia. The mixture was concentrated in vacuo to about 50 mL and cooled, and the solid was collected by filtration and washed with ethanol. The amides were used in subsequent reactions without further purification.

**4-Oxo-4*H*-pyrimido[2,1-*b*]benzazolecarboxamides (8c and 13). General Method C. Table II.** The appropriate carboxylic acid (**6c** or **11**; 10 mmol) was refluxed for 2 h in 100 mL of thionyl chloride. The solvent was removed in vacuo, and the residue was suspended three times in 75 mL of anhydrous benzene and concentrated in vacuo, in order to remove traces of thionyl chloride. The residue was suspended in 50 mL of anhydrous diglyme, $NH_3$ was bubbled into the mixture for 20 min, and the mixture was stirred for an additional 2 h. The solid was collected by filtration, washed thoroughly with water, and dried. The amides were used in subsequent reactions without further purification.

**4-Oxo-4*H*-pyrimido[2,1-*b*]benzazolecarbonitriles (9 and 14). General Method D. Table II.** The amide (**8** or **13**; 20 mmol) was suspended in 150 mL of anhydrous DMF, $PCl_5$ (5.0 g, 24 mmol) was added, and the mixture was stirred for 2 h at 40–50 °C. The reaction mixture was poured into ~600 mL of ice–water to yield a solid, which was collected by filtration, washed thoroughly (first with saturated aqueous $NaHCO_3$, then with water), and dried. The nitriles were used in subsequent reactions without further purification.

**Tetrazol-5-yl-4-oxo-4*H*-pyrimido[2,1-*b*]benzazoles (10 and**

(12) Other workers have reported the PCA activity of compounds **12a**[6a] and **15a**[6b,c] when administered either intravenously or orally, apparently as an aqueous solution of the sodium or potassium salt. These workers report oral activity at the 0.1 mg/kg level, although they do not indicate the activity of a reference agent, such as doxantrazole, in their assays for comparative purposes. In our assay, we find these two compounds to be inactive orally at 10 mg/kg when administered as a suspension in Klucel, compared with a MED of 5 mg/kg for doxantrazole when administered this way. Other than the difference in the dosing vehicle or some other variation in the technical details of our PCA assay, we have no explanation for the discrepancy in these results.

15). **General Method E.** A mixture of the nitrile (**9**, **14a**, or **14c**; 10 mmol), sodium azide (0.85 g, 13 mmol), and ammonium chloride (0.70 g, 13 mmol) in 100 mL of anhydrous DMF was heated at 120–130 °C for either 1 day (for the 2-substituted compounds **9**) or 4 days (for the 3-substituted cases **14a** and **14c**). The reaction mixture was cooled, poured into 500 mL of ice–water, and acidified with concentrated HCl to yield a solid, which was collected by filtration and recrystallized from DMF–water to give the pure tetrazole **10** or **15**.

**3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzoxazol-4-one (15b).** A mixture of 2-aminobenzoxazole (6.70 g, 50.0 mmol), ethyl 1*H*-tetrazol-5-ylacetate[10] (7.80 g, 50.0 mmol), and triethyl orthoformate (10.0 g, 67.8 mmol) was heated at 120 °C briefly to obtain a stirrable melt. $AlCl_3$ (0.3 g, 2 mmol) was added, and the mixture was heated at 120 °C in an open flask for 40 min. The mixture was cooled and triturated with methanol, and the solid was collected by filtration and washed with methanol to give 10.9 g (73%) of the intermediate ester **17** as a light yellow solid, mp 202–203 °C. This ester (2.00 g, 6.67 mmol) was combined with 8 g of polyphosphoric acid, heated to 140 °C gradually over 1 h, held at 140 °C for 20 min, then cooled somewhat, and treated with 100 mL of water. The resulting solid was collected by filtration, washed thoroughly with water, and dried to give 1.05 g (62%) of yellow solid. Recrystallization from DMF–water gave 0.63 g (37%; 27% overall) of the pure tetrazole **15b**.

**Acknowledgment.** We thank Prof. R. F. Borch and Dr. J. F. Gerster for helpful discussions and Ms. J. A. Sneitzer for assistance with the manuscript.

**Registry No.** **4a**, 58099-49-3; **4b**, 69461-78-5; **6a**, 69461-82-1; **6b**, 69461-84-3; **6c**, 69461-85-4; **7a**, 84712-10-7; **7b**, 84712-11-8; **7c**, 84712-12-9; **8a**, 84712-20-9; **8b**, 84712-21-0; **8c**, 84712-22-1; **9a**, 84712-23-2; **9b**, 84712-24-3; **9c**, 84712-25-4; **10a**, 84712-13-0; **10b**, 84712-14-1; **10c**, 84712-15-2; **11a**, 21786-97-0; **11b**, 69461-83-2; **11c**, 50532-94-0; **12a**, 64483-80-3; **12b**, 84712-16-3; **12c**, 84712-17-4; **13a**, 84712-26-5; **13b**, 84712-27-6; **13c**, 84712-28-7; **14a**, 21787-05-3; **14b**, 84712-29-8; **14c**, 84712-30-1; **15a**, 73351-75-4; **15b**, 84712-18-5; **15c**, 84712-19-6; **16**, 13616-37-0; **17**, 84731-12-4; DMAF, 7542-94-1; 2-aminobenzothiazole, 136-95-8; 2-aminobenzoxazole, 4570-41-6; 2-amino-1-methylbenzimidazole, 1622-57-7; diethyl (ethoxymethylene)malonate, 87-13-8; 5-aminotetrazole, 4418-61-5; ammonia, 7664-41-7; triethyl orthoformate, 122-51-0.

# Antimycotic Azoles. 6. Synthesis and Antifungal Properties of Terconazole, a Novel Triazole Ketal

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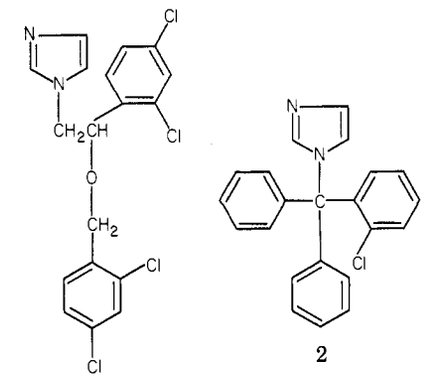
The preparation and antifungal properties of *cis*-1-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine are reported. Terconazole has a high topical in vivo activity against vaginal candidosis in rats and against dermatophytosis in guinea pigs.

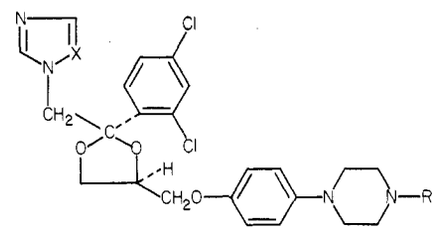
Miconazole (**1**),[1,2] clotrimazole (**2**),[3] and ketoconazole (**3a**)[4,7] are widely used for the treatment of fungal diseases. Unlike miconazole and clotrimazole, ketoconazole is well absorbed in the bloodstream. After oral administration, ketoconazole has been found to be highly effective against crop candidosis in turkeys, vaginal candidosis in rats, systemic candidosis in chickens, systemic and skin candidosis, as well as dermatophytosis, in guinea pigs, and coccidioidomycosis in mice.[6]

As a result of our continuous search for new antifungal agents, in particular azole ketals, having an improved topical activity against superficial fungal infections, we report the synthesis and antifungal properties of terconazole (**3b**), a novel triazole ketal.

**Chemistry.** The synthesis, starting from *cis*-[2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl]methyl benzoate (**4**),[4] is outlined in Scheme I. The sodium salt of triazole, generated in situ from triazole and NaH dispersion (50%), in mineral oil is coupled with the bromomethyl ketal **4** in $Me_2SO$ at 130 °C to give a mixture of triazole derivatives, which are saponified at reflux temperature with NaOH in dioxane–water to the alcohols **5** and **6**. Pure **5** and **6** are obtained after chromatography



**1** **2**



**3a**, X = CH; R = $COCH_3$
**b**, X = N; R = $CH(CH_3)_2$

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