ized with 2 N HCl. The mixture was evaporated *in vacuo* to a small volume (~5 ml). The product was precipitated by addition of water and was collected by filtration. The crude product was recrystallized twice from water to give 0.43 g (83%) of 9-β-D-arabinofuranosyl-2-methylthioadenine (**5**) as needles: mp 245–247°; $[\alpha]^{25}D$ +48.6° (*c* 1.0, DMF); uv λ_{max} (pH 1) 208 and 268 nm (ε 22,100 and 17,500); λ_{max} (pH 7) 233 and 273 nm (ε 21,600 and 15,600); λ_{max} (pH 11) 234 and 274 nm (ε 21,400 and 15,900). *Anal.* ($C_{11}H_{15}N_5O_4S$) C, H, N.

9-β-D-Arabinofuranoxyl-2-benzyloxyadenine (6). A solution of 9-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-2-chloroadenine (**1**, 1.72 g, 3 mmol) in benzyl alcohol (30 ml) containing sodium (0.21 g) was heated for 19 hr at 160–165°. The reaction mixture was cooled and diluted with chloroform (250 ml). The chloroform solution was washed with water (2 × 250 ml), then with 2 N HCl (2 × 250 ml), and finally with water (3 × 250 ml) before drying over Na_2SO_4. Silica gel (30 g) was added to the chloroform solution, and the mixture was evaporated *in vacuo* to dryness. The crude reaction product absorbed on silica gel was applied to the top of a silica gel column; elution with petroleum ether removed benzyl alcohol and the benzylated product was eluted with ethyl acetate–dichloromethane (3:7). The syrupy benzylated product was dissolved in 2-methoxyethanol (35 ml), and 10% palladium on charcoal (0.3 g) was added to the solution. The mixture was hydrogenated under 3 atm of pressure for 24 hr at room temperature before the palladium catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in a mixture of 15 ml of concentrated NH_4OH and 300 ml of water. Volume reduction *in vacuo* to 100 ml caused crystallization of the product. Recrystallization in the same manner gave 0.38 g (34%) of 9-β-D-arabinofuranosyl-2-benzyloxyadenine as needles: mp 275–280° dec; $[\alpha]^{25}D$ +6.0° (*c* 1, DMSO); uv λ_{max} (pH 1) 287 nm (ε 18,800); λ_{max} (pH 7) 248 and 295 nm (ε 9700 and 13,500); λ_{max} (pH 11) 226 and 286 nm (ε 16,100 and 15,300) *Anal.* ($C_{17}H_{19}N_5O_5$) C, H, N.

Hydrolysis of **6** with 1.75 N hydrochloric acid for 15 min at 65° and paper chromatographic analysis of the hydrolysis mixture [Whatman No. 1, descending, 4:1:5 (upper phase) *l*-butanol–ethanol–water] showed the presence of D-arabinose and absence of any benzylated D-arabinose.

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Notes

Synthesis and Antifungal Properties of 3-Substituted *as*-Triazino[5,6-*c*]quinolines

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Several 3-substituted *as*-triazino[5,6-*c*]quinolines (**1**, **2**, and **3**) have been found to possess antifungal activity[1] (Table II). The synthesis of the *as*-triazino[5,6-*c*]quinolines, which represent a new heterocyclic ring structure, is also described in this paper.

Chemistry. A synthetic route (Scheme I) to the 3-substituted *as*-triazino[5,6-*c*]quinolines (**1**, **2**, and **3**), similar to that used in the preparation of pyrimido[5,4-*e*]-*as*-triazines,[2] has been developed. The reaction of ethyl carbazate with the known 3-nitro-4-chloroquinoline (**4**) (a modification of the procedure of Bachman, *et al.*[3]) afforded the intermediate ethyl 3-(3-nitro-4-quinolyl)carbazate hydrochloride (**5**). Subsequent reduction of the nitro group of **5** gave ethyl 3-(3-amino-4-quinolyl)carbazate hydrochloride (**6**). Ring closure of **6** to *as*-triazino[5,6-*c*]quinolin-3(4*H*)-one (**9**) was accomplished by two different routes.

Treatment of **6** in EtOH with NaOMe in the presence of air afforded the sodium salt **7**. Subsequent acidification of **7** with AcOH gave **9**.

The second route to **9** was through the ring closure of **6** in hot AcOH to the intermediate 1,2-dihydro-*as*-triazino-[5,6-*c*]quinolin-3(4*H*)-one hydrochloride (**8**). Oxidation of **8** with $Pb(OAc)_4$ in AcOH gave **9**.

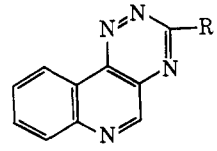
The chlorination (with $POCl_3$) of **9** provided the intermediate 3-chloro-*as*-triazine[5,6-*c*]quinoline (**1**), from which the 3-amino-*as*-triazino[5,6-*c*]quinolines (**2**) were prepared by facile chloro displacement with the appropriate amine. The compound 3-methoxy-*as*-triazino[5,6-*c*]quinoline (**3**) was obtained by chloro displacement of **1** with NaOMe in MeOH.

Mycology. The 3-substituted *as*-triazino[5,6-*c*]quinolines (**1**, **2a–c**, and **3**) (Table I), initially screened against *Candida albicans* and *Microsporum canis* by the agar diffusion-cylinder cup method,[4] were found to inhibit the growth of these organisms (Table II).

Compounds **1**, **2a–c**, and **3** were also screened in a minimum inhibitory concentration test against the following species of yeasts: *Torulopsis glabrata*, *Candida tropicalis*, *C. krusei*, *C. guillermondi*, and *C. albicans* (Table II). Against all organisms the 3-chloro (**1**) compound was consistently more active than the other compounds (**2a–c** and **3**), all of which showed a similar degree of activity. Also, compound **1** was as active as the known antifungal agent Nystatin.

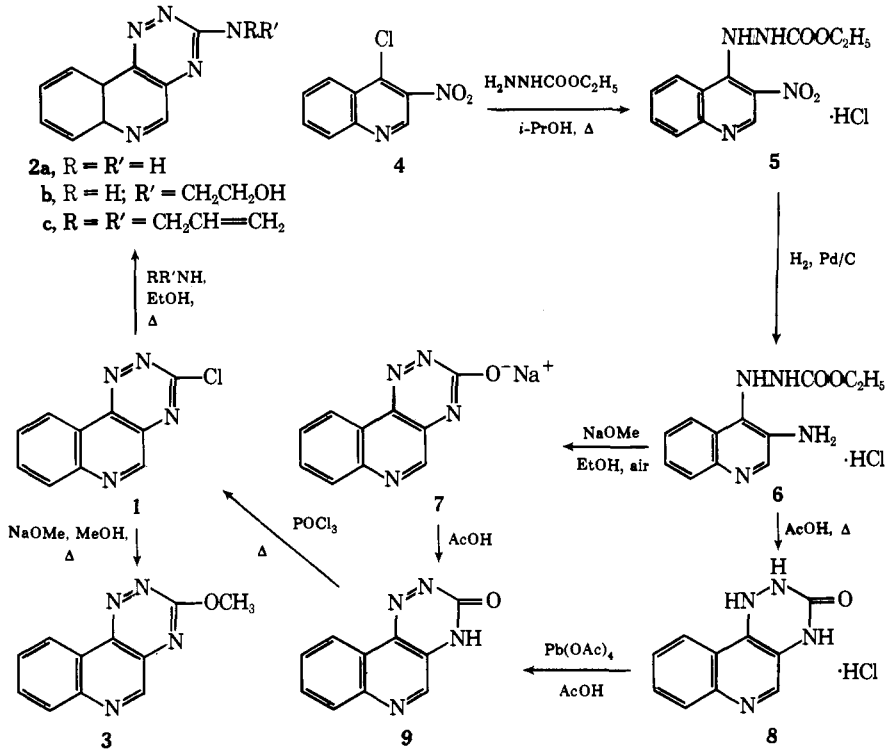
In an agar dilution test[5] the 3-chloro (**1**) derivative showed complete inhibition of *Aspergillus niger* at 10

Table I. Triazinoquinolines



No.	R	Mp, °C	Yield, %	Formula	Analyses
1	Cl	173–174	56	$C_{10}H_5ClN_4$	C, H, Cl, N
2a	NH_2	>300	88	$C_{10}H_7N_5$	C, H, N
2b	$NHCH_2CH_2OH$	215–220	74	$C_{12}H_{11}N_5O$	C, H, N
2c	$N(CH_2CH{=}CH_2)$	69.5–70.5	7	$C_{16}H_{15}N_5$	C, H, N
3	OCH_3	165–168	75	$C_{11}H_8N_4O$	C, H, N

Scheme I



μg/ml of medium, while the other derivatives (**2a–c, 3**) showed complete inhibition at 100 μg/ml and were inactive at 10 μg/ml.

Experimental Section

Melting points were determined on a Fisher-Johns (hot stage) apparatus and are uncorrected. The infrared spectra were determined on a Perkin-Elmer Infracord 137B. Elemental analyses were determined on all compounds to within ±0.4% of the theoretical values.

4-Chloro-3-nitroquinoline[3] **(4).** A mixture of 3-nitro-4-quinolinol (201 g, 1.06 mol) and $POCl_3$ (537 ml) was treated with PCl_5 (223 g, 1.06 mol) with mechanical stirring. The reaction mixture was heated gradually to 90° over 40 min, refluxed (110–112°) for 4.5 hr, and then cooled in an ice bath for 40 min. The resultant light tan solid was collected by filtration, washed with cold cyclohexane (9 × 20 ml), and dried in a vacuum desiccator: mp 123–125° (lit.[3] mp 121–122°); yield 210 g (95%).

Ethyl 3-(3-Nitro-4-quinolyl)carbazate Hydrochloride (5). Freshly prepared 4† (210 g, 1.01 mol) was added to *i*-PrOH (2000 ml); a temperature rise of 10° was observed. The mixture was treated with ethyl carbazate (105 g, 1.01 mol) at 25–30° with mechanical stirring. The reaction mixture was heated on a steam bath for 50 min and then stored in the refrigerator overnight. The resultant light tan solid was collected and washed with *i*-PrOH (2 × 125 ml) and Et_2O: mp 201–203° dec; yield 234 g (75%). *Anal.* ($C_{12}H_{12}N_4O_4$·HCl) C, H, N.

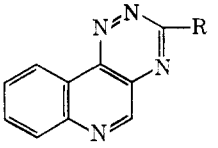
†The metastable 4 should be used within 3 hr of its preparation.

Ethyl 3-(3-Amino-4-quinolyl)carbazate Hydrochloride (6). A mixture of **5** (73 g, 0.22 mol), 5% Pd/C (4.8 g, with 50% H_2O), and 95% EtOH (MeOH) was hydrogenated in a Parr apparatus; hydrogen uptake was 93% of theory in 1 hr. The reaction mixture was stored in the refrigerator overnight, and the crude product was collected by filtration and washed with 95% EtOH (MeOH) (5 × 20 ml) and Et_2O (2 × 100 ml), mp 210°. Recrystallization from MeOH (1000 ml) gave 6: mp 241–246° dec; yield 34 g (55%). *Anal.* ($C_{12}H_{14}N_4O_2$·HCl) C, H, N.

1,2-Dihydro-*as*-triazino[5,6-*c*]quinolin-3(4*H*)-one Hydrochloride (8). Compound **6** (40 g, 0.14 mol) was gradually added to AcOH (480 ml), heated to reflux in 20 min, and maintained at reflux for 50 min, with mechanical stirring. The reaction mixture was allowed to cool to 50° over 20 min and to 15° over 1 hr. An orange solid was collected by filtration and washed with *i*-PrOH (10 × 10 ml) and Et_2O (3 × 100 ml): mp 285–298° dec; yield 21 g (61%); ir (Nujol) 5.86 μ (C=O). *Anal.* ($C_{10}H_8N_4O$·HCl) C, H, N.

***as*-Triazino[5,6-*c*]quinolin-3-ol Sodium Salt (7).** A mixture of **6,** (185 g, 0.65 mol) and MeOH (1052 ml) was treated with a rapid stream of dry air for 10 min with mechanical stirring. Then a solution of NaOMe (94 g, 1.74 mol) in 95% EtOH (MeOH) (560 ml) was added to the reaction mixture at 5–10° in 40 min. The reaction temperature was allowed to warm to 25–27° over a period of 1.5 hr, as the flow of dry air was continued. The addition of air was discontinued and the mixture was cooled in an ice bath for 2

Table II. Triazinoquinolines. Antifungal Activity



No.	R	MIC[a] in Sabouraud's dextrose broth: *T. glabrata* (VM-22)[b]	*C. tropicalis* (VM-25)[b]	*C. krusei* (VM-29B)[b]	*C. guillermondi* (VM-42)[b]	*C. albicans* (VM-71)[b]	*C. albicans* (VM-81)[b]	*C. albicans* (M-3)[b]
1	Cl	≤10	≤10	≤10	≤10	≤10	≤10	≤10
2a	NH_2	30	>50	10	>50	30	40	30
2b	$NHCH_2CH_2OH$	30	>50	20	>50	30	50	40
2c	$N(CH_2CH{=}CH_2)_2$	40	>50	20	30	40	50	50
3	OCH_3	40	40	20	30	40	40	20
Nystatin[c]		≤10	≤10	≤10	≤10	≤10	≤10	≤10

[a]Minimal inhibitory concentration, μg/ml, dissolved in *N,N*-dimethylacetamide (ref 4). [b]Norwich Pharmacal culture number. [c]Potency = 4162 units/mg.

hr. The resultant bright yellow solid was collected by filtration and washed with 95% EtOH (MeOH) (3 × 50 ml), *i*-PrOH (3 × 50 ml), and Et_2O (3 × 250 ml): yield 190 g (theory, 141 g of **7** plus 37 g of NaCl).

***as*-Triazino[5,6-*c*]quinolin-3(4*H*)-one (9). Method A.** To AcOH (760 ml) at 15–20° was added **7** (with residual NaCl) (190 g) with mechanical stirring. The reaction mixture was allowed to warm to room temperature in 2 hr and then cooled to 17° for 2 hr. A yellow, crystalline solid was collected by filtration and washed with *i*-PrOH (5 × 100 ml) and Et_2O (5 × 200 ml): mp 305–313° dec; yield 158 g (theory, 129 g plus 37 g of NaCl). Recrystallization three times from AcOH gave **9**: mp 284–294° dec; ir (Nujol) 5.93 μ (C=O). *Anal.* ($C_{10}H_6N_4O$) C, H, N.

Method B. A mixture of **8** (0.6 g) and AcOH (20 ml) was treated with $Pb(OAc)_4$ (4.0 g), and the reaction mixture was stirred at room temperature for 1 hr. The resultant solid was collected by filtration and washed with AcOH, *i*-PrOH, and Et_2O. Recrystallization from AcOH gave **9**; the infrared absorption was identical with **9** prepared by method A.

3-Chloro-*as*-triazino[5,6-*c*]quinoline (1). Compound **9** (35 g, 0.16 mol) was added to $POCl_3$ (150 ml) at 20–25° with rapid stirring. The mixture was heated to 100° in 10 min, maintained at 102–105° for 7 min, and then cooled rapidly to 2–5°. The cooled reaction mixture was poured into ice (1300 g) with rapid stirring, allowed to warm to 15° over 1 hr, and then cooled an additional 1 hr in an ice bath. Solid product was collected by filtration and washed with H_2O (5 × 80 ml). The air-dried product was further dried in a vacuum desiccator over Drierite, mp 171–181° dec; recrystallization from EtOAc gave **1**.

3-Amino-*as*-triazino[5,6-*c*]quinoline (2a). A mixture of **1** (10 g, 0.05 mol) and 95% EtOH (MeOH) (190 ml) was treated with a stream of dry NH_3 for 45 min at 35–45°, with rapid stirring. The reaction mixture was cooled in an ice bath for 1 hr, and the resultant bright yellow, crystalline solid was collected by filtration and washed with 95% EtOH (Et_2O) (6 × 10 ml) and Et_2O. An analytical sample was prepared by recrystallization from 90% DMF (MeOH).

Compounds **2b** and **2c** were prepared by the same procedure as described for that of **2a**.

3-Methoxy-*as*-triazino[5,6-*c*]quinoline (3). A mixture of **1** (44 g, 0.20 mol) and a solution of NaOMe (11 g, 0.20 mol) in MeOH (2000 ml) was refluxed for 1 hr and then filtered hot. The cooled filtrate was filtered to give **3**, mp 163–167°. An analytical sample was prepared by recrystallization from MeOH.

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Radiopharmaceuticals. 12. A New Rapid Synthesis of Carbon-11 Labeled Norepinephrine Hydrochloride†

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The rapid growth in the use of radiopharmaceuticals for external radioscanning has resulted in an increasing need for new safer radiopharmaceuticals labeled with elements emitting radiation which can be detected outside the body barrier. The potential impact of organ-specific radiopharmaceuticals labeled with short-lived nuclides on the safety of diagnostic procedures has justified expending considerable effort in the development of rapid organic synthetic procedures in order to accomplish the incorporation of simple labeled precursors into relatively complex molecules of pharmacological interest.[1,2]

One of the more potentially useful radionuclides for labeling is ^{11}C which decays by positron emission and has a half-life of 20.4 min. The advantage of ^{11}C for diagnostic procedures lies in its short half-life (which lowers the radiation dose to the patient) and positron emission (which offers improved resolution on scanning by detection of the 511-keV annihilation radiation). In addition, since carbon is naturally occurring the properties of the normal bioactive molecules are not significantly altered by labeling. However, the reduced time scale in which one must work, as well as the limited number of readily available ^{11}C-labeled precursor molecules[1] (for example ^{11}CO, $^{11}CO_2$, $^{11}CH_2O$, $H^{11}CN$, $H^{11}C \equiv {}^{11}CH$, etc.), presents certain restrictions on the nature of the ^{11}C-labeled radiopharmaceuticals which one can prepare employing syntheses described in the chemical literature.

Presently there is considerable interest in developing an agent which would localize in the myocardium and thus aid in the diagnosis of myocardial infarction. Tracer studies with both ^{14}C and ^{3}H have shown that norepinephrine rapidly localizes in heart tissue.[3,4] This suggested that

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