Reactivity of the A-CH=N-NR-CX-B System. 4-Methyl-5-hydroxy-5-phenyl- (or thienyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3-ones and their Ring Contraction Products

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Received June 23, 1978

The behaviour of some monosemicarbazones of phenyl- (**1a-c**) and thienyl-glyoxal (**2a-c**) towards cyclizing agents has been investigated. Upon aqueous sodium hydroxide treatment, 4-methyl-semicarbazones **1a** and **2a** gave the addition products **3** and **4**, respectively, whereas the 2-methyl- and 2,4-dimethyl derivatives **1b,c** and **2b,c** gave demolition products only. On the other hand, compounds **1b,c** gave the addition product **8** and the triazine **7**, respectively, on treatment with aqueous hydrochloric acid.

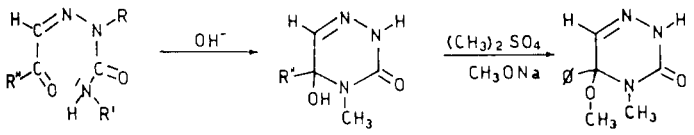
Bromination of **1a,b** gave the bromosemicarbazone **10a** and a mixture of **10b** and **9**, respectively. Performing the same reaction on **3** and **4** at 115°, the 1,3,4-oxadiazoles **13** and **14** have been obtained.

The behaviour of bromosemicarbazones [**10a,b**] and of the bromo-tetrahydrotriazine **9** towards heating or treatment with base has also been investigated.

J. Heterocyclic Chem., 16, 145 (1979).

Following our research on the reactivity of the A-CH=N-NR-CX-B system towards cyclizing agents (1), in this paper we report the behaviour of some monosemicarbazones of phenyl- (**1a-c**) and thienyl-glyoxal (**2a-c**), variously substituted in the semicarbazidic residue (see Scheme I).

Scheme I



1a-c, **2a-c** — **3,4** — **5**

1a-c, **3**: R" = C_6H_5

2a-c, **4**: R" = 

a: R = H; R' = CH_3

b: R = R' = CH_3

c: R = CH_3; R' = H

The sodium hydroxide action on **1a** and **2a** monosemicarbazones produces a tetrahydro-1,2,4-triazine cyclization, giving the compounds **3** and **4**, respectively. The structures have been assigned on the basis of analytical and spectroscopic data. The mass spectra of **3** and **4** exhibit, besides the molecular ion, the presence of the $(M-17)^+$ peak. Moreover, in the nmr spectrum of **3**, five singlets at δ 2.55, 6.42, 7.12, 7.30, and 10.60 can be seen for the N-CH_3, CH, OH, Ph, and NH protons, respectively. The aromatic protons singlet is peculiar for a phenyl bound to an sp^3 carbon atom. In the starting compound **1a**, the aromatic protons appear as a multiplet 2 + 3 because of the carbonyl anysotropy. Methylation of **3** by dimethylsulfate and sodium methoxide gives the *O*-methyl derivative **5**, whose structure is confirmed by the nmr spectrum (2).

In contrast with the two foregoing derivatives, the action of sodium hydroxide on the 2,4-dimethyl- (**1b,2b**) and 2-methyl-semicarbazones (**1c,2c**) gives hydrolytic demolition products only.

As to the behaviour towards acids (aqueous hydrochloric acid) of the phenyl-glyoxal-semicarbazones **1a-c**, we have observed a reactivity similar to that reported (3) for the corresponding thienyl-glyoxal derivatives (towards hydrobromic acid/acetic acid). Namely, from compound **1c** we obtained the triazine **7**, and from compound **1b** we obtained the addition product **8**, whereas **1a** was recovered unchanged.

Even towards bromination with bromine and sodium acetate in acetic acid, the semicarbazones **1a-c** behave like the corresponding thienyl-glyoxal-semicarbazones (3). The results we obtained are as follows: (i) from **1a**, as described (4), the bromo-semicarbazone **10a** is obtained. It can be isolated even in the absence of sodium acetate in the reaction mixture; (ii) compound **1b** afforded a mixture of the bromo-semicarbazone **10b** and the bromo-tetrahydrotriazine **9**. The latter compound was obtained even spontaneously from **10b**. Performing the reaction in the absence of sodium acetate, in the reaction mixture we found the unbrominated derivative **8**; (iii) the derivative **1c** remained unchanged.

The structures **7**, **8**, **9**, and **10b** are supported by analytical, chemical (see Scheme II) and spectroscopic (see Experimental) data (5).

In an attempt to obtain the corresponding bromo derivatives, we have investigated the bromination reaction on the tetrahydrotriazines **3** and **4** with bromine and sodium acetate in acetic acid. We have observed that compounds **3** and **4** do not react at room temperature.

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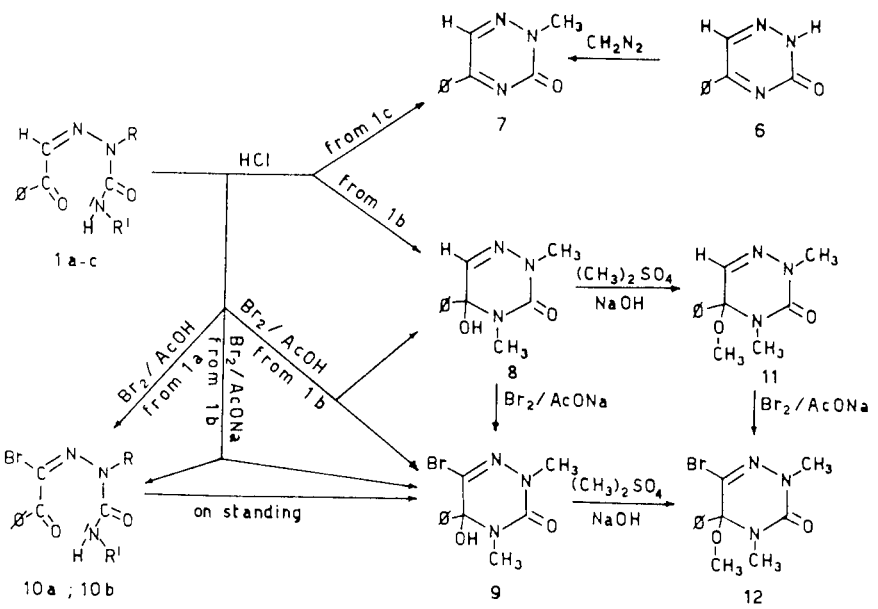
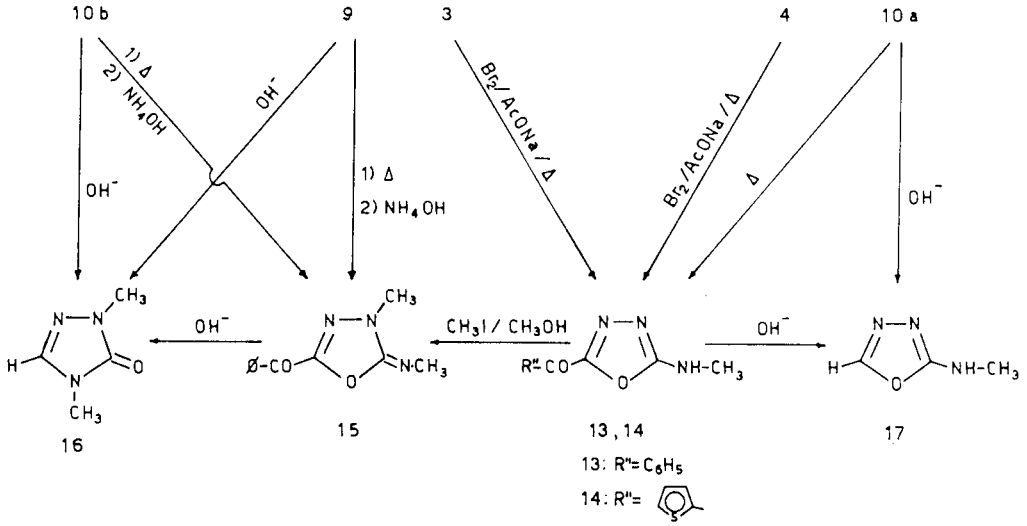
Scheme II



Scheme III



On the other hand, performing the bromination reaction at 115°, it was possible to obtain the corresponding 2-methylamino-5-benzoyl(thenoyl)-1,3,4-oxadiazoles **13** and **14**. Keeping in mind that upon heating the bromo-semicarbazone **10a** or brominating at high temperature the semicarbazones **1a** and **2a** with bromine and sodium acetate in acetic acid, we obtained compounds **13** and **14**, respectively, it is possible to think that **3** and **4** in the reaction mixture are in equilibrium with the semicarbazone open form.

The acyl-1,3,4-oxadiazoles **13** and **14**, upon treatment with base undergo acyl replacement (3), forming compound **17**. The latter compound can be obtained even directly from the bromo-semicarbazone **10a** by treatment with base.

The methylation of **13** with methyl iodide in methanol involves the heterocyclic nitrogen atom giving the oxadiazolinic derivative **15**. From this derivative, upon treatment with base, the triazolone **16** was obtained (6). The oxadiazoline **15** was also obtained by heating, in absence of any solvent, the bromotetrahydrotriazine **9** or the corresponding bromosemicarbazone **10b**. Moreover, upon aqueous sodium hydroxide treatment, compounds **9** and **10b** gave the same triazolone derivative **16** (see Scheme III) (7).

EXPERIMENTAL

All melting points (Kofler) are uncorrected. The infrared spectra (Nujol) were obtained using a Perkin-Elmer 137 infracord spectrophotometer. The nuclear magnetic resonance spectra were obtained with a Jeol C-60 H spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained on Perkin-Elmer 270 spectrometer. Phenylglyoxal was obtained from Fluka A. G.; the 2-methyl-, 4-methyl-, and 2,4-dimethyl semicarbazides were obtained as reported in the literature (8); the 4-methyl-monosemicarbazone of phenylglyoxal was obtained as reported in the literature (4); the 2-methyl-, 4-methyl-, and 2,4-dimethylmonosemicarbazones of α-thienylglyoxal were obtained as reported in the literature (3).

Preparation of the Monosemicarbazones **1b,c**. General Procedure.

To a stirred solution of phenylglyoxal (0.08 mole) in ethanol (25 ml.), water (180 ml.) and acetic acid (2 ml.), at 50°, the appropriate semicarbazide (0.08 mole) was added. After standing for 24 hours, the reaction mixture was filtered and the crude product thus obtained was recrystallized from the appropriate solvent. Yields and physical data are as follows.

Compound **1b**.

This compound, obtained in 90% yield, had m.p. 120° (benzene-ligroin); ir: 3356 (NH), 1685 and 1639 cm^{-1} (C=O); nmr (DMSO-d_6): 2.77 δ (d, 3H, $NHCH_3$, J = 4.5 Hz), 3.34 (s, 3H, NCH_3), 6.94 (q, 1H, $NHCH_3$, J = 4.5 Hz), 7.40-8.20 (m, 6H, Ar-H, CH).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.11; H, 5.98; N, 19.35.

Compound **1c**.

This compound, obtained in 85% yield, had m.p. 157-158° (ethyl acetate); ir: 3413, 3125 (NH_2), 1706 and 1642 cm^{-1} (C=O); nmr (DMSO-d_6): 3.29 δ (s, 3H, NCH_3), 6.68 (br.s, 2H, NH_2), 7.25-8.10 (m, 6H, ArH, CH).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.56; H, 5.66; N, 20.36.

Reaction of **1a-c** and **2a-c** with Sodium Hydroxide. General Procedure.

Two grams of the product was treated in 15 ml. of 10% aqueous sodium hydroxide at room temperature, and allowed to stand for 30 minutes. Cold water (45 ml.) was added with stirring and the solution acidified with 10% hydrochloric acid.

Compound **3**.

The crude product obtained from **1a**, which precipitated as a white solid, was removed by filtration (1.8 g.), and crystallized from ethyl acetate, yielding **3**, m.p. 182-184°; ir: 3226 (NH, OH) and 1634 cm^{-1} (C=O); nmr (DMSO-d_6); 2.55 δ (s, 3H, NCH_3), 6.42 (s, 1H, CH), 7.12 (s, 1H, OH), 7.30 (s, 5H, ArH), 10.50 (s, 1H, NH); ms: 205 $(M)^+$, 188, 177, 161, 147, 128, 118, 105, 100, 91, 78, 77.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.56; H, 5.28; N, 20.42.

Compound **4**.

The crude product obtained from **2a** (1.7 g.) was chromatographed on a dry column of silica gel (cyclohexane-ethyl acetate 1:1 as eluent) giving **4**, m.p. 161-162°; ir: 3257 (NH), 3058 (OH) and 1658 cm^{-1} (C=O); nmr (DMSO-d_6); 2.68 δ (s, 3H, NCH_3), 6.58 (s, 1H, CH), 7.01 (m, 2H, H_3, H_4), 7.41 (s, 1H, OH), 7.54 (q, H_5, J = 5.3 Hz, J = 1.9 Hz), 10.76 (s, 1H, NH).

Anal. Calcd. for $C_8H_9N_3O_2S$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.15; H, 4.10; N, 20.05.

Compounds **1b**, **1c**, **2b**, and **2c** gave decomposition products.

Reaction of **1a-c**, **8**, and **11** with Bromine-Sodium Acetate. General Procedure.

To a solution of the product (0.01227 mole) in acetic acid (17.5 ml.) at room temperature, anhydrous sodium acetate (4 g.) was added and then, dropwise and with stirring, 6.6 ml. of a cooled solution of bromine in acetic acid (prepared from 5.50 ml. of bromine in 50 ml. of acetic acid) were added. The reaction mixture was stirred for 30 minutes (3 hours for **8**), then diluted with water, and the crude product collected by filtration.

The crude material (2.8 g.) obtained from **1a** (2.5 g.), after crystallization from benzene gave **10a**, m.p. 155-156° as already reported (4).

The crude material (3.02 g.) obtained from **1b** (2.68 g.) was treated at room temperature with ethyl acetate and filtered. The insoluble fraction, recrystallized from ethyl acetate gave **9** (2.2 g.), m.p. 190-191°; ir: 3195 (OH) and 1639 cm^{-1} (C=O); nmr (DMSO-d_6): 2.57, 3.34 δ (2s, 6H, $2NCH_3$), 7.40 (s, 5H, ArH), 7.79 (s, 1H, OH); ms: 297 $(M)^+$, 280, 267, 254, 239, 223, 218, 191, 140, 134, 118, 105, 103, 89, 83, 77.

Anal. Calcd. for $C_{11}H_{12}BrN_3O_2$: C, 44.31; H, 4.05; N, 14.09; Br, 26.80. Found: C, 44.29; H, 4.20; N, 14.14; Br, 26.69.

The ethyl acetate solution was evaporated to dryness at room temperature and the residue (0.75 g.), recrystallized from ligroin gave **10b** (0.44 g.), m.p. 92-93°; ir: 3367 (NH), 1709 and 1672 cm^{-1} (C=O); nmr (deuteriochloroform): 2.71 δ (d, 3H, $NHCH_3$, J = 4.8 Hz), 3.83 (s, 3H, NCH_3), 5.70 (br. signal, 1H, $NHCH_3$), 7.45-8.30 (m, 5H, ArH).

Anal. Calcd. for $C_{11}H_{12}BrN_3O_2$: C, 44.31; H, 4.05; N, 14.09; Br, 26.80. Found: C, 44.20; H, 3.90; N, 14.15; Br, 26.68.

This compound, allowed to stand for several weeks, led to **9**. Compound **1c** was recovered unchanged.

Use of the general procedure described above on compound **8** (2.68 g.) gave **9** (2.45 g.).

Use of the general procedure described above on compound **11** (2.85 g.) gave **12** (1.32 g.), m.p. 90° (ligroin); ir: 1664 cm^{-1} (C=O); nmr (DMSO-d_6): 2.57, 3.33 δ (2s, 6H, $2NCH_3$), 3.43 (s, 3H, OCH_3), 7.56 (s, 5H, ArH); ms: 311 $(M)^+$, 280, 266, 253, 232, 216, 205, 175, 162, 146, 129, 118, 105, 91, 83, 77.

Anal. Calcd. for $C_{12}H_{14}BrN_3O_2$: C, 46.17; H, 4.52; N, 13.46; Br, 25.60. Found: C, 46.06; H, 4.47; N, 13.37; Br, 25.30.

Reaction of **1a-c** with Bromine-Acetic Acid. General Procedure.

To 0.00614 mole of the product, dissolved in 9 ml. of acetic acid, dropwise and with stirring 3.4 ml. of acetic solution of bromine (prepared as above), were added, and the mixture allowed to stand for 48 hours.

From **1b** (1.35 g.) the crude product collected to pump (0.85 g.) was shown to contain a mixture of **8** and **9**. The crude material was treated with warm water and filtered. The insoluble fraction (0.55 g.) was identified as triazine **9**; the aqueous liquor mother, after neutralization with aqueous ammonium hydroxide, was extracted with chloroform, dried and evaporated. After crystallization from benzene-ligroin, **8** (0.06 g.) was obtained.

In the case of **1a** (1.25 g.) dilution with water of the reaction mixture gave **10a** (0.35 g.).

In the case of **1c**, starting material was recovered.

Reaction of **1a-c** with Hydrochloric Acid. General Procedure.

A suspension of the semicarbazone (0.01 mole) in aqueous hydrochloric acid 1:10 (25 ml.) was refluxed (30 minutes for **1a**

and **1c**; 5 minutes for **1b**). After cooling, the crude material was collected and washed with water.

Compound **1a** was recovered unchanged.

The crude product (1.75 g.) obtained from **1b** (2.20 g.), was suspended in aqueous sodium hydroxide solution (5%) and filtered. The insoluble fraction was identified as **1b** unchanged. Acidification of the alkaline solution with hydrochloric acid (1:1) gave **8** (0.85 g.), m.p. 172-174° (benzene-ligroin); ir: 3165 (OH) and 1637 cm^{-1} (C=O); nmr (deuteriochloroform): 2.78, 3.43 δ (2s, 6H, $2NCH_3$), 5.73 (s, 1H, OH), 6.57 (s, 1H, CH), 7.43 (s, 5H, ArH).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.13; H, 6.01; N, 19.24.

Compound **1c** (2.05 g.) gave **7** (1.35 g.), m.p. 159-160° (water); ir: 1667 cm^{-1} (C=O); nmr (DMSO-d_6): 3.70 δ (s, 3H, NCH_3), 7.40-8.30 (m, 5H, ArH), 8.72 (s, 1H, CH).

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.10; H, 4.94; N, 22.58.

Reaction of **3** and **4** with Bromine-Sodium Acetate with Heating.

To a solution of the product (1.25 g.) in acetic acid (9 ml.) at 115° were added anhydrous sodium acetate (2 g.), and, dropwise and with stirring, an acetic solution of bromine (prepared as above) (3.5 ml.). After cooling, dilution with water (60 ml.) and standing for four hours, the crude material was collected and washed with water.

Compound **3** gave 2-methylamino-5-benzoyl-1,3,4-oxadiazole **13** (0.5 g.), m.p. 155° (4).

Compound **4** gave 2-methylamino-5-thenoyl-1,3,4-oxadiazole **14** (0.62 g.), m.p. 203° (3).

Heating of **8**, **9**, **10a**, and **10b**. General Procedure.

The product (0.005 mole) was placed in a 5 ml. pear shaped flask, and the flask was immersed in an oil bath. The temperature of the bath was increased until melting of the product. After cooling, the crude material was dissolved in warm water, and filtered.

In the case of **9**, **10a**, and **10b**, the solution was neutralized with aqueous ammonium hydroxide 1:1.

Compound **8** was recovered unchanged.

Compound **10a** gave the 2-methylamino-5-benzoyl-1,3,4-oxadiazole **13** (50%).

The product obtained from **9** and **10b** recrystallized from ligroin was identified as 2-benzoyl-4-methyl-5-methylimino-Δ^2-1,3,4-oxadiazoline **15** (yield 30% from **9**, and 80% from **10b**), m.p. 139-140°; ir: 1721 (C=N) (9) and 1645 cm^{-1} (C=O); nmr (deuteriochloroform): 3.13, 3.50 δ (2s, 6H, $2NCH_3$), 7.32-8.43 (m, 5H, ArH); ms: 217 $(M)^+$, 131, 112, 105, 77, 70, 69, 51, 43.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.66; H, 5.02; N, 19.28.

Reaction with Sodium Hydroxide of **9**, **10a**, **10b**, **13**, **14**, and **15**.

Compound **16**.

Three g. of **9** in 20 ml. of 10% aqueous sodium hydroxide were refluxed for two hours. After extraction with chloroform and evaporation of the solvent 0.9 g. of **16** were obtained. By acidification of alkaline solution, 1.42 g. of crude product were obtained. This, dissolved in sodium bicarbonate solution (12.5 ml. at 10%), allowed to separate unchanged **9** (0.6 g.) from benzoic acid (0.68 g.).

Compound **10b** (0.75 g.) suspended in 5 ml. of 10% aqueous sodium hydroxide were allowed to stand until solution. After dilution (5 ml. of water), the alkaline solution was extracted with chloroform, dried, and evaporated. The crude product (0.25 g.) was identified as **16** (6). Acidification of the mother alkaline solution with hydrochloric acid (1:1), gave benzoic acid (0.22 g.).

A suspension of **15** (0.95 g.) in ethanol (15 ml.), and 10% aqueous sodium hydroxide (4 ml.) was allowed to stand for 12 hours at room temperature. Without heating, the solvent was evaporated and after dilution with water, the alkaline solution was extracted with chloroform. Evaporation of the solvent gave **16** (0.44 g.) (6). Acidification of the alkaline solution with hydrochloric acid 1:1 gave benzoic acid (0.48 g.).

Compound **17**.

Compound **10a** (4.5 g.) was suspended in 50 ml. of 5% aqueous sodium hydroxide until solution. The alkaline solution was extracted with ethyl acetate, dried, and evaporated. The crude product (0.7 g.) was identified as **17** (10). Acidification of the mother liquor with hydrochloric acid 1:1 gave benzoic acid (1.65 g.).

A suspension of **13** (or **14**) (0.01 mole) in ethanol (25 ml.) and 10% aqueous sodium hydroxide (6 ml.) was refluxed for 30 minutes. After evaporation of the solvent, and dilution with water, the solution was extracted with chloroform, dried, and evaporated. The crude product (0.15 g. from **13**, and 0.30 g. from **14**) was identified as 2-methylamino-1,3,4-oxadiazole **17**. By acidification of the mother alkaline solution with hydrochloric acid 1:1, gave benzoic acid (1.05 g. from **13**) and thenoic acid (1.2 g. from **14**).

Methylation of **3**, **6**, **8**, **9**, and **13**.

Compound **5**.

A mixture of **3** (1.02 g.), dimethyl sulfate (0.5 ml.) and sodium methoxide (from 0.13 g. of sodium) in anhydrous methanol (10 ml.) was refluxed for 8 hours. The solvent was evaporated and the residue diluted with water, filtered and washed with water. The crude product (0.55 g.) recrystallized from benzene-ligroin gave **5**, m.p. 161-162°; ir: 3205 (NH) and 1689 cm^{-1} (C=O); nmr (DMSO-d_6): 2.52 δ (s, 3H, NCH_3), 3.20 (s, 3H, OCH_3), 6.46 (s, 1H, CH), 7.38 (s, 5H, ArH), 10.90 (s, 1H, NH); ms: 219 $(M)^+$, 204, 188, 175, 161, 142, 130, 118, 105, 102, 91, 77.

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.29; H, 6.00; N, 19.00.

Compound **7**.

To a suspension of **6** (2 g.) (11) in methanol-water 10:1 (30 ml.), an excess of ethereal solution of diazomethane was added. After standing 24 hours the solvent was evaporated and the product collected; it was identical in all respects with an authentic sample of **7** (see before).

Compound **11**.

A mixture of **8** (4.1 g.), aqueous 10% sodium hydroxide (25 ml.) and dimethyl sulfate (2.4 ml.) was heated in a water bath for 90 minutes with stirring. After dilution with water, the mixture was extracted with chloroform, which was washed with aqueous 5% sodium hydroxide, dried and evaporated. The residue gave **11** (1.6 g.), b.p. 124° at 0.8 mm Hg; ir: 1672 cm^{-1} (C=O); nmr (deuteriochloroform): 2.70, 3.30 δ (2s, 6H, $2NCH_3$), 3.46 (s, 3H, OCH_3), 6.34 (s, 1H, CH), 7.41 (s, 5H, ArH).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.78; H, 6.48; N, 18.02. Found: C, 61.65; H, 6.40; N, 17.91.

Compound **12**.

To a solution of **9** (1.5 g.) in aqueous 10% sodium hydroxide (5 ml.), dimethylsulfate (0.6 ml.) was added and the mixture was stirred at room temperature for 4 hours. After dilution with water the crude material was collected (1 g.) and crystallized from ligroin, affording **12**. Acidification of the alkaline solution gave 0.5 g. of **9** unchanged.

Compound **15**.

A suspension of **13** (1.2 g.) and methyl iodide (1.2 ml.) in methanol (15 ml.) was refluxed for 8 hours. After removing the solvent, dilution with water and filtration gave **13** unchanged. Neutralization of the aqueous solution with aqueous ammonium hydroxide 1:1 gave **15** (0.08 g.).

REFERENCES AND NOTES

(1) G. Werber, F. Buccheri, N. Vivona and M. Gentile, *J. Heterocyclic Chem.*, 14, 1433 (1977) and references cited therein.

(2) The uv spectra of compounds **3** and **5** are almost identical, showing a maximum at 242 nm.

(3) G. Werber, F. Buccheri, N. Vivona and M. Gentile, *J. Heterocyclic Chem.*, 15, 1393 (1978).

(4) G. Werber, F. Buccheri and M. L. Marino, *Ann. Chim. (Rome)*, 62, 11 (1972).

(5) The uv spectra of **6** and **7** exhibit a maximum at 288 and 292 nm, respectively; the compounds **11** and **8** exhibit uv spectra which nearly overlap with a maximum at 253 nm.

(6) C. F. Kröger, P. Seldtiz and M. Mutscher, *Chem. Ber.*, 98, 3034 (1965).

(7) A similar behaviour has been observed for the corresponding 5-thienyl-substituted bromo-tetrahydrotriazine and thienyl-glyoxal bromo-semicarbazone. See paper quoted in reference (3).

(8) C. Vogelesang, *Rec. Trav. Chim.*, 62, 5 (1943).

(9) H. Najer, J. Menin and J. F. Giudicelli, *Compt. Rend.*, **258**, 4579 (1964); J. F. Giudicelli, J. Menin and H. Najer, *Bull. Soc. Chim. France*, 4568 (1968).

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(11) L. Wolff, *Ann. Chem.*, 325, 151 (1902).