$1710 \text{ cm}^{-1}$  indicating that the compounds were predominantly in the keto form.

The use of Raney Ni in alkaline medium for the replacement of SH by H gave the desired product with II, but with I simultaneous dechlorination also took place. This was confirmed by its identity with the desulfurization product of 4-ethyl-5-phenyl-4H-1,2,4-triazole-3-thiol. The use of 20% HNO<sub>3</sub> for desulfurization, however, gave the desired products with both I and II being obtained in better yields and purity.

 $N^1$ ,  $N^4$ -disubstituted thiosemicarbazides (Table I) were prepared by literature methods and were cyclized to obtain the required triazoles (Table II).

Hypoglycemic Activity.—The majority of the compounds in the present series possessed hypoglycemic activity. The replacement of SH in I and II by H or OH either reduced or eliminated the activity. Their SEt derivatives (11 and 15) were fairly active while the other thioethers were much less active. Among the alkylsulfonyl analogs, Me derivatives (17 and 21) showed some activity, but the higher homologs were inactive. Interchange of the alkyl and aryl groups at positions 4 and 5 of II rendered it (35) completely inactive.

The replacement of *p*-chlorophenyl or *p*-sulfamoylphenyl groups by H considerably reduced the activity. However, when this replacement was with Me (**33**), the activity was pronounced and maintained for a long period (50.9% lowering at 24 hr), but the acute toxicity study of this compound and the other more active ones in this series (**11**, **17**, **24**, **33**, and **34**) revealed that they were toxic.

## **Experimental Section**

Screening Method.—The hypoglycemic activity was tested in normal, fasting, albino rats weighing 180-200 g. The drug was administered orally as suspension in 2% gum acacia at a dose level of 25 mg/kg and blood sugar was determined at 1.5, 3, 5, 7, 9, and 24 hr by Somogyi's method<sup>3</sup> using Nelson's reagent.<sup>4</sup>

**Chemistry.**<sup>5</sup>—*p*-Chlorophenylacetic acid has been obtained in 43% yield from *p*-chloroacetophenone following a modified Wilgerodt reaction,<sup>6</sup> mp 104-105° (lit.<sup>7</sup> mp 103-105°). Anal. (C<sub>8</sub>H<sub>7</sub>ClO<sub>2</sub>) C, H.

**4-Ethyl-5**-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole.—4-Ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole-3-thiol (1.42 g) dissolved in 3% NaHCO<sub>3</sub> was heated with activated Raney Ni (W-6, *ca*. 3 g) under reflux for 4 hr, cooled, neutralized (HCl), and extd (Et<sub>2</sub>O). The product remaining after removal of the solvent was isolated as hydrochloride.

Action of Raney Ni on 5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,-4-triazole-3-thiol.—5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3thiol (1.5 g) when treated with activated Raney Ni as above gave a cryst product ( $\text{Et}_2\text{O}-C_6\text{H}_{14}$ ): yield 0.33 g (30%); mp 115–116°. This was identified as 4-ethyl-5-phenyl-4*H*-1,2,4-triazole, by mmp with an authentic sample prepd from 4-ethyl-5-phenyl-4*H*-1,2,4-triazole-3-thiol by desulfurization with Raney Ni. *Anal.* ( $C_{11}\text{H}_{11}\text{N}_{3}$ ) C, H, N.

5-p-Chlorophenyl-4-ethyl-4H-1,2,4-triazole.—5-p-Chlorophenyl-4-ethyl-4H-1,2,4-triazole-3-thiol (1.5 g) was added in small batches to dil HNO<sub>3</sub> (40 ml of 20%) not allowing the temp to rise above 45°. The reaction mixt was maintained at 50°

(7) (a) P. Petrenko-Kritschenko, Ber., 25, 2240 (1892); (b) F. von Straus, Justus Liebigs Ann. Chem., 393, 317 (1912). for a further 15 min, cooled, basified (NaOH), and extd (Et<sub>2</sub>O). The combined exts were washed (H<sub>2</sub>O) and dried (Na<sub>2</sub>SO<sub>4</sub>) and Et<sub>2</sub>O was removed to obtain the title compound: crystd (Et<sub>2</sub>O-C<sub>6</sub>H<sub>14</sub>); yield, 0.93 g.

4-Ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole was similarly prepared from 4-ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole-3-thiol in good yields.

5-p-Chlorophenyl-4-ethyl-4H-1,2,4-triazole-3-sulfonic Acid. 5-p-Chlorophenyl-4-ethyl-4H-1,2,6-triazole-3-thiol (2.4 g) dissolved in 8% aq NaOH (25 ml) was treated with H<sub>2</sub>O<sub>2</sub> (7.5 ml of 30%), maintaining the temp at 50-60° for 1 hr. It was then cooled and acidified with HCl (pH 4), and the solid was collected by filtration and crystd (H<sub>2</sub>O).

5-p-Chlorophenyl-4-ethyl-3-methylthio-4H-1,2,4-triazole.— MeI (2 ml, 0.32 mole) was added to 5-p-chlorophenyl-4-ethyl-4H-1,2,4-triazole-3-thiol (5.9 g, 0.25 mole) dissolved in dil aq NaOH and stirred vigorously for 15 min during which turbidity developed and suddenly a white solid sepd. After allowing it to stand for 1 hr, the solid was collected by filtration, washed (H<sub>2</sub>O), dried, and crystd (EtOH); yield 3.8 g.

5-p-Chlorophenyl-4-ethyl-3-methylsulfonyl-4H-1,2,4-triazole. -5-p-Chlorophenyl-4-ethyl-3-methylthio-4H-1,2,4-triazole (1.0 g) dissolved in AcOH (15 ml) was treated with H<sub>2</sub>O<sub>2</sub> (3 ml of 30%) by heating on a steam bath for 90 min. Additional H<sub>2</sub>O<sub>2</sub> (1 ml) was added and heated for a further 30 min. The mixt was then evapd to dryness under reduced pressure and the residue crystd (EtOH) to get white shining needles. Oxidation with KMnO<sub>4</sub> in AcOH gave the same product in 50% yield.

5-p-Chlorophenyl-4-ethyl-3-hydroxy-4H-1,2,4-triazole.—5-p-Chlorophenyl-4-ethyl-3-methylsulfonyl-4H-1,2,4-triazole (1.43 g) was refluxed with NaOMe in MeOH (0.28 g of Na in 25 ml of MeOH) for 8 hr. MeOH was distd off and the residue was dissolved in H<sub>2</sub>O, neutralized with HCl (pH 7.5), and evapd to dryness. The residue was extd with EtOH and crystd (80% EtOH) to yield white needles; yield, 0.68 g.

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## Benzocycloalka[1,2-c]pyridazones

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The varied pharmacological activities that have been reported by Laborit and coworkers<sup>1</sup> for the phenylpyridazone system V have prompted us to investigate the potential of this structural combination in a more con-



strained framework. The possibility then existed that the less flexible arrangement would lead to more specific and/or more potent activity.

**Chemistry.**—All the pyridazones listed in Table I were prepared by the synthetic route shown in Scheme I. The most efficient route to the N-substituted pyr-

<sup>(3)</sup> M. Somogyi, J. Biol. Chem., 160, 69 (1945).

<sup>(4)</sup> N. Nelson, ibid., 153, 375 (1944).

<sup>(5)</sup> The melting points were taken in open capillary tubes with partial immersion thermometer and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within 0.4% of the theoretical values.

<sup>(6)</sup> E. Schwenk and E. Bloch, J. Amer. Chem. Soc., 64, 3051 (1942).

 <sup>(</sup>a) H. Laborit, C. G. Wermuth, B. Weber, B. Delbane, C. Chekler,
 C. Baron, and H. Rosengarten, Agressologie, 6, 415 (1965).
 (b) H. Laborit,
 B. Weber, C. Baron, B. Delbane, and H. Pavlovichova, *ibid.*, 6, 463 (1965).
 (c) H. Laborit, B. Weber, B. Delbane, and C. Baron, *ibid.*, 6, 483 (1965).

## TABLE I

2-Substituted-5,6-dihydrobenzo[ $\hbar$ ]cinnolin-3(2H)-ones and 2-Substituted-2,5,6,7-tetrahydro-3H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-ones



|           |   |          |                              | Crystn               |   |              |                     |
|-----------|---|----------|------------------------------|----------------------|---|--------------|---------------------|
| No.       | R   | n        | Mp, °C                       | solvent <sup>a</sup> | Formula   | $Analyses^b$ | Method <sup>c</sup> |
| 1         | H   | 1        | 257-261                      | A                    | $C_{12}H_{10}N_2O$                                  | C, H, N      | Α                   |
| <b>2</b>  | $CH_3$  | 1        | 120-122                      | В                    | $C_{13}H_{12}N_2O$                                  | Ν            | Ba                  |
| 3         | $C_2H_5$  | 1        | 71-73                        | В                    | $C_{14}H_{14}N_2O$                                  | C, H, N      | Ba                  |
| 4         | $CH_2CH_2Cl$  | 1        | 94-95                        | C-D                  | $C_{14}H_{13}ClN_2O$                                | C, H, Cl     | Ba                  |
| <b>5</b>  | $CH_2C_6H_5$  | 1        | 105 - 108                    | В                    | $C_{19}H_{16}N_2O$                                  | C, H, N      | Bc                  |
| 6         | $CH_2CH_2C_6H_5$  | 1        | 86-88                        | в                    | $C_{20}H_{18}N_2O$                                  | С, Н, N      | Bb                  |
| 7         | $CH_2COC_eH_5$  | 1        | 185 - 187                    | Α                    | $\mathrm{C_{20}H_{16}N_{2}O_{2}}$                   | C, H, N      | Bc                  |
| 8         | CH <sub>2</sub> C=CH  | 1        | 144-146                      | C-D                  | $C_{15}H_{12}N_2O$                                  | Ν            | $\mathbf{Bc}$       |
| 9         | $\mathrm{CH}_{2}\mathrm{CH}_{2}(\mathrm{C}_{4}\mathrm{H}_{8}\mathrm{NO})\cdot\mathrm{HCl}\cdot0.25\mathrm{H}_{2}\mathrm{O}^{d}$ | 1        | 235-236                      | С                    | $C_{18}H_{21}N_{3}O_{2} \cdot HCl \cdot 0.25H_{2}O$ | C, H, N, Cl  | Ca                  |
| 10        | $(CH_2)_3N(CH_3)_2 \cdot HCl \cdot 0.75H_2O$  | 1        | 174-176                      | E-F                  | $C_{17}H_{21}N_{3}O \cdot HCl \cdot 0.75H_{2}O$     | C, H, N, Cl  | Ca                  |
| 11        | $\mathrm{CH_{2}CH_{2}(C_{4}H_{8}N) \cdot HCl \cdot 0.5H_{2}O^{e}}$  | 1        | 216 - 218                    | C-F                  | $C_{18}H_{21}N_{3}O \cdot HCl \cdot 0.5H_{2}O$      | C, H, N, Cl  | Ca                  |
| 12        | $CH_2CH_2CH(CH_3)_2$  | 1        | $160 \ (0.2 \text{ mm})^{f}$ |                      | $C_{17}H_{20}N_2O$                                  | С, Н, N      | $\mathbf{Bb}$       |
| 13        | $\mathrm{CH}_{2}\mathrm{CH}_{2}(\mathrm{C}_{5}\mathrm{H}_{10}\mathrm{N})^{g}$   | 1        | 114-116                      | Н                    | $C_{19}H_{23}N_2O$                                  | C, H, N      | Ca                  |
| 14        | $\mathrm{CH}_{2}\mathrm{CH}_{2}\mathrm{N}(\mathrm{CH}_{3})_{2}\cdot\mathrm{HCl}$  | 1        | 201-202                      | E-F                  | $C_{16}H_{19}N_{3}O \cdot HCl$                      | C, H, N, Cl  | Bb                  |
| 15        | $CH_2CH_2(C_5H_{11}N_2)\cdot 2HCl\cdot 0.5H_2O^h$   | 1        | 258 - 260                    | C-F                  | $C_{19}H_{24}N_4O \cdot 2HCl \cdot 0.5H_2O$         | C, H, N, Cl  | Cb                  |
| 16        | Н   | <b>2</b> | 235 - 239                    | $\mathbf{E}$         | $C_{13}H_{12}N_2O$                                  | C, H, N      | Α                   |
| 17        | $CH_3$  | <b>2</b> | 115 - 117                    | G-B                  | $C_{14}H_{14}N_2O$                                  | C, H, N      | Bb                  |
| 18        | $C_2H_5$  | <b>2</b> | 96-97                        | В                    | $C_{15}H_{16}N_2O$                                  | C, H, N      | Bb                  |
| 19        | $CH_2CH_2C_6H_5$  | <b>2</b> | 92 - 95                      | G-B                  | $C_{21}H_{20}N_2O$                                  | C, H, N      | Bb                  |
| <b>20</b> | CH <sub>2</sub> C=CH  | <b>2</b> | 105-107                      | G-B                  | $C_{16}H_{14}N_2O$                                  | C, H, N      | Bb                  |
| <b>21</b> | $CH_2CH_2(C_5H_{10}N)^{g}$  | <b>2</b> | 98-100                       | В                    | $C_{20}H_{25}N_{3}O$                                | С, Н, N      | Cb                  |
| 22        | $(\mathrm{CH}_2)_3\mathrm{N}(\mathrm{CH}_3)_2\cdot\mathrm{HCl}$   | <b>2</b> | 226 - 228                    | C-F                  | $C_{18}H_{23}N_3O \cdot HCl$                        | C, H, N, Cl  | Ca                  |

<sup>a</sup> A = EtOH, B = Skellysolve B (bp 60-80°), C = *i*-PrOH, D = H<sub>2</sub>O, E = MeCN, F = Et<sub>2</sub>O, G = EtOAc, H = cyclohexane. <sup>b</sup> Analytical results obtained for the indicated elements were within  $\pm 0.3\%$  of the calcd values. <sup>c</sup> See Experimental Section. <sup>d</sup> C<sub>4</sub>H<sub>8</sub>NO = morpholino. <sup>c</sup> C<sub>4</sub>H<sub>8</sub>N = pyrrolidino. <sup>d</sup> Compds 12 and 26 were purified by evaporative distn. <sup>d</sup> C<sub>5</sub>H<sub>10</sub>N = piperidino. <sup>h</sup> C<sub>5</sub>H<sub>11</sub>N<sub>2</sub> = 4-methylpiperazino.

|     |               |              | TABLE I   | E  |                      |                       |                        |
|-----|---------------|--------------|---|--|----------------------|-----------------------|------------------------|
|     |               | 2-Substitu   | TED-4,4a,5,6-TETRAHYDROBEN                        | zo[h]cinnolii                            | N-3(2 $H$ )-ONES AND |                       |                        |
|     | 2-Substitutei | -2,4,4a,5,6, | 7-неханудго-2-метну <mark>l-</mark> 3 <i>H</i> -3 | BENZO[6,7]CYC                            | lohepta[1,2-c]pyri   | dazin-3-ones          |                        |
|     |               |              |   |  |                      |                       |                        |
| No. | R             | n            | Mp, °C  | )<br>R<br>Crystn<br>solvent <sup>a</sup> | Formula              | Analyses <sup>b</sup> | Method                 |
| 23  | H             | 1            | 199-201 <sup>d</sup>                              | $\mathbf{E}$                             | $C_{12}H_{12}N_{2}O$ | C, H, N               | D                      |
| 24  | H             | <b>2</b>     | 186–188 <sup>d</sup>                              | Α  | $C_{13}H_{14}N_2O$   | C, H, N               | D                      |
| 25  | $CH_3$        | 1            | <b>99–</b> 101                                    | A-D                                      | $C_{13}H_{14}N_{2}O$ | C, H, N               | $\mathbf{E}\mathbf{b}$ |
| 26  | $CH_3$        | <b>2</b>     | 110–115 (0.15 mm) <sup>e</sup>                    |  | $C_{14}H_{16}N_2O$   | C, H, N               | $\mathbf{E}\mathbf{b}$ |
| 27  | $CH_2C_6H_5$  | 1            | 82-84   | В  | $C_{19}H_{18}N_2O$   | C, H, N               | Ea                     |

<sup>a-c</sup> See footnotes in Table I. <sup>d</sup> Initially described by H. M. Holava and R. A. Partyka, U. S. Patent 3,464,988 (1969). \* See footnote f, Table I.

idazones IV involved alkylation of the readily available key intermediate III. Thus, the known keto acid Ia<sup>2</sup> afforded on treatment with hydrazine hydrate a high yield of the pyridazinone IIa which was oxidized effectively with  $Br_2$  in AcOH<sup>3</sup> to the corresponding pyridazone IIIa in excellent yield. Alkylations of the <sup>(2)</sup> W. H. Puterbaugh and R. L. Readshaw, J. Amer. Chem. Soc., **82**, 3635 (1960).

pyridazone IIIa, with the appropriate reagents, proceeded with ease when a NaH dispersion in mineral oil was used with DMF as the solvent.

Carbonyl absorption in the expected region in the ir clearly demonstrated that alkylation proceeded on N.

(3) (a) F. G. Baddar, N. Latif, and A. A. Nada, J. Chem. Soc., 7005 (1965).
 (b) W. G. Overend and L. F. Wiggins, *ibid.*, 239 (1947).



Further evidence of the homogeneity of the alkylated products was indicated by their nmr (60 MHz) spectra. Equally good results were obtained for the higher homologs (b series) where the keto acid  $Ib^4$  was the starting material.

Compound 2 was also prepared by initially alkylating the pyridazinone IIa with MeI followed by oxidation with  $Br_2$  in AcOH to the pyridazone IV. This approach, although successful, was not as efficient as the sequence shown. Compounds 25 and 27 were prepared by the reaction of the appropriate alkylhydrazine with keto acid Ia. This approach, however, is also not as desirable as the route described originally because of the relative inaccessibility of the requisite alkyl hydrazines and the generation of a larger number of intermediate derivatives.

Use of 4 as an alkylating agent was unsuccessful when attempted with several secondary amines under varied conditions.

All the compounds described herein were evaluated for analgetic, hypotensive, antiinflammatory, and CNS activities. The analgetic activity was evaluated according to the mouse hot plate procedure of Eddy and Leimbach.<sup>5</sup> Hypotensive activity was determined in unanesthetized, normotensive rats with indwelling carotid catheters. Blood pressure was measured at definite time intervals by means of a Statham pressure transducer (P23Gb) and recorder. Antiinflammatory activity was evaluated in rats by the carrageenininduced foot edema method of Winter.<sup>6</sup> CNS effects such as depression or stimulation were determined in mice employing a modification of Irwin's technique.<sup>7</sup> the reserpine ptosis reversal procedure.<sup>8</sup> Neuroleptic activity was determined in rats employing standard conditioned avoidance techniques. An apparatus similar to that of Cook and Weidley<sup>9</sup> was utilized. All the compounds were found to be devoid of significant biological activity as determined by the above mentioned techniques.

## Experimental Section<sup>10</sup>

General Methods for the Preparation of Compounds 1-22. Method A.--Compounds 23 or 24 were dissolved in warmed (70°) AcOH to which was added a molar equiv of  $Br_2$  at such a rate to control the vigorous evolution of HBr. Heating was maintained at 70° for 1.5 hr after all  $Br_2$  was added. The cooled reaction mixt was poured into cold  $H_2O$  and the pptd product filtered, washed well with  $H_2O$ , and recrystd.

Method B.—To a soln of III (a or b) (0.01 mole) in 50 ml of DMF was added NaH<sup>10</sup> (0.01 mole) and the resulting mixt was allowed to stir for 40 min at room temp. The appropriate alkyl halide (0.011 mole) was added and stirring was continued for 2-3 hr thereafter at room temp.

**a**.—The reaction mixt was poured into  $H_2O$  and extd with  $Et_2O$ . The extracts were washed with  $H_2O$  and brine. After having been dried (Na<sub>2</sub>SO<sub>4</sub>), the  $Et_2O$  was removed and the crude product was purified by recrystn.

**b.**—The reaction mixt was poured into  $H_2O$  and worked up as in Ba above. The crude product was dissolved in MeCN and washed with pentane to remove the mineral oil. If necessary, decolorization with C was carried out. The MeCN was then removed and the product purified by recrystn.<sup>11</sup>

c.—The reaction mixt was poured into  $H_2O$  and the pptd product was collected, washed with  $H_2O$ , dried, washed with pentane, and redried.

**Method C.**—To a soln of III (a or b) (0.015 mole) in 30 ml of DMF was added NaH<sup>10,12</sup> (0.032 mole) and the resulting reaction mixt was allowed to stir at room temp for 30 min. The appropriate aminoalkyl halide HCl was added and stirring was continued at 85° for 3 hr thereafter. The reaction mixt was worked up as described in Bb.

**a.**—The crude product was converted into its HCl salt which was then recrystd.<sup>13</sup>

**b.**—The crude product was chromatographed on alumina after which its HCl salt was prepd and recrystd.<sup>13</sup>

General Methods for the Preparation of Compounds 23-27. Method D.—The appropriate keto acid I was combined with a molar equiv of hydrazine hydrate in EtOH. After having refluxed for 2 hr, the soln was cooled and the cryst product was filtered, washed with cold EtOH, and recrystd.

Method E.—The appropriate keto acid I (0.03 mole) and alkylhydrazine (0.04 mole) were combined in 50 ml of 95% EtOH and refluxed for 3 hr.

**a.**—The soln was poured into  $H_2O$  and extd with  $Et_2O$ . The extracts were worked up in the usual manner.

 $b.{-\!\!\!-} H_2O$  was added and the cryst product filtered, washed, and dried.  $^{11}$ 

**Acknowledgments.**—Thanks are due to the pharmacology, analytical, and spectroscopic departments of Bristol Laboratories for their services.

(8) L. O. Randall and R. E. Bagdon, Ann. N. Y. Acad. Sci., 80, 626 (1959).

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(10) Melting points were determined in a Mel-Temp apparatus and are uncorrected. Nmr and ir spectra were obtained on all compds and were consistent with structure. Where NaH is used, it indicates a dispersion of ca. 50% in mineral oil.

- (11) Compounds 12 and 26 were purified by evaporative distn. Compound 14 was chromatographed on alumina before its HCl salt was prepd.
  - (12) NaH (3 equiv) must be used in the prepn of 15.
  - (13) Salts of 13 and 21 were not prepd.

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