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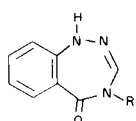
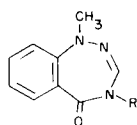
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The chemical behavior of 4-methyl and 4-phenyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepines towards methylating and acidic agents has been investigated. The 4-methyl derivative, when treated with methyl fluorosulfonate furnished, after crystallization from water, a quaternary salt (2,4-dimethyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepinium fluorosulfonate), whereas from the 4-phenyl derivative, a complex mixture was obtained, which, after boiling with water, afforded 2-methylindazolone, aniline fluorosulfonate and formic acid. In acidic medium the 4-methyl derivative underwent an isomerization reaction yielding 1-imino-3-methylquinazolin-4-one, but the 4-phenyl derivative exclusively yielded products resulting from ring opening. In alkaline medium, both compounds gave hydrolytic cleavage products.

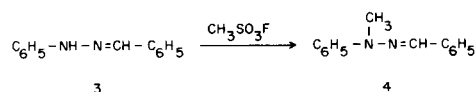
J. Heterocyclic Chem., **16**, 1411 (1979).

Recently we reported the synthesis of compounds containing a 1,2,4-benzotriazepine ring (2). In connection with these studies it was desirable to investigate a pathway to 1-methylated-1,2,4-benzotriazepines **2**, considering the analogy between these compounds and the well known drugs of the 1,4-benzodiazepine series.

R = CH₃ (1a)R = C₆H₅ (1b)R = CH₃ (2a)R = C₆H₅ (2b)

We point out in this type of molecule the presence of the phenylhydrazone group, which generally exhibits poor reactivity towards alkylating agents. The examples reported in the literature concerning the methylation of benzaldehyde phenylhydrazone describe the use of dimethylsulfonium methylide (3) and of dimethylloxosulfonium methylide (4) as methylating agents.

N-alkylation of phenylhydrazones has also been reported by Kenyon, *et al.*, in anhydrous ammonia containing sodium or potassium amide (5). More recently, A. Jonczyk, *et al.*, described an alkylation procedure in aqueous medium in the presence of tetrabutylammonium chloride as a catalyst (6). We found in preliminary experiments that benzaldehyde phenylhydrazone **3**, when treated with methyl fluorosulfonate, furnished the corresponding *N*-methyl derivative **4** in moderate yield.

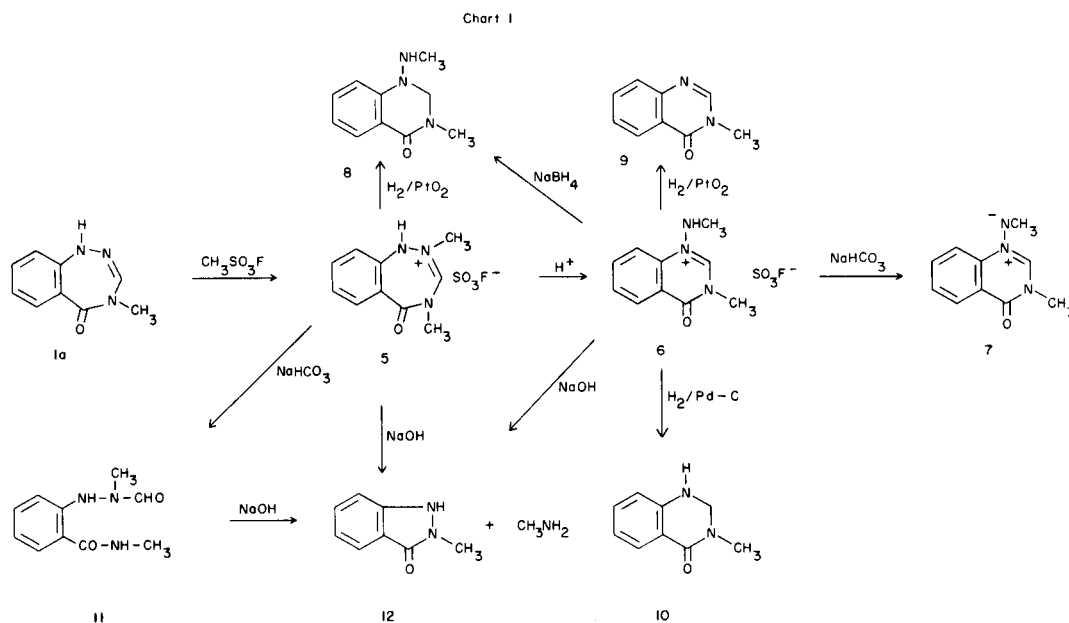


This result prompted us to submit 4-methyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine **1a** and 4-phenyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine **1b** to reaction with methyl fluorosulfonate in an aprotic medium (benzene) at room temperature, after verifying the inertness of these compounds towards conventional methylating agents such as methyl iodide, dimethylsulfate, diazomethane.

Results and discussion.

The reaction of **1a** did not yield the expected 1,4-dimethyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine **2a**, but instead the quaternary salt **5** was isolated after crystallization from water (Chart I). The structure of compound **5** (2,4-dimethyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepinium fluorosulfonate) was assigned on the basis of elemental and nmr analysis and chemical properties (see Experimental). This compound was quite stable when dry, but it rapidly underwent an isomerization process with ring contraction and production of 1-methylimino-3-methyl-4-oxoquinazolinium fluorosulfonate **6** (Chart I) in aqueous acidic medium or more slowly on standing in the open air. The latter quaternary salt, treated with sodium bicarbonate solution, furnished 1-methylimino-3-methylquinazolin-4-one **7**, whose dipolar structure is in accordance with its physical properties (high m.p., very low solubility) (7). The quinazolone structure of **6** was also demonstrated through reduction by sodium borohydride which yielded 1-methylamino-3-methyltetrahydroquinazolin-4-one **8**. This structure was confirmed by analytical and nmr data. The same compound was directly obtainable from the quaternary salt **5** by catalytic hydrogenation in the presence of platinum oxide.

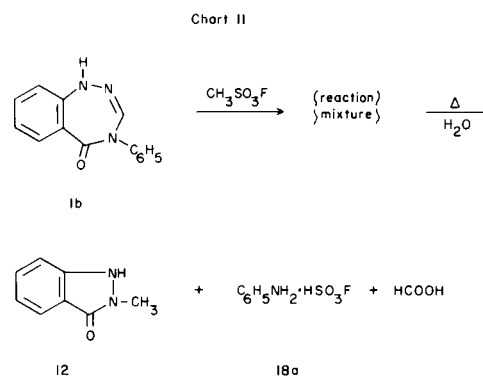
On the other hand, catalytic reduction of **6** led to fission



of the exocyclic N-N bond resulting in a deamination process. In the presence of platinum oxide, 3-methylquinazolin-4-one **9** was obtained, whereas, in the presence of palladium on carbon, the deamination was accompanied by reduction of the C=N double bond, leading to the formation of 3-methyltetrahydroquinazolin-4-one **10**. Hydrogenation of the betaine **7** was not possible, probably owing to its very low solubility. The quaternary salt **5** appeared extremely sensitive to alkaline agents; treatment at room temperature even with diluted sodium bicarbonate solution involved nucleophilic attack on the carbon atom at position 3. Since the cyclic aminal intermediate is not stable, the 1,2,4-benzotriazepine ring was cleaved giving *N*-methyl-*N*-formyl-*o*-hydrazinobenzoic acid methylamide **11**.

The latter compound was hydrolyzed by more drastic treatment with warm sodium hydroxide solution and then again cyclized leading to 2-methylindazolone **12** and methylamine, supplying further evidence that the methylation of **5** did not occur at position 1. The 2-methylindazolone **12** was also directly obtained by warming the quaternary salt **5** with dilute sodium hydroxide, as well as from the salt **6**, presumably proceeding also in this case through the open structure **11**.

Similar attempts at the methylation of 4-phenyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine **1b** by methyl fluorosulfonate resulted in the isolation of a crude reaction product, which appeared by tlc analysis to be a complex mixture of at least four compounds. It was not possible to purify this mixture either in the acidic or in the basic state. On warming the mixture in water, it furnished 2-methylindazolone **12**, aniline fluorosulfonate **18a** and formic acid (Chart II). In this case the formation of a

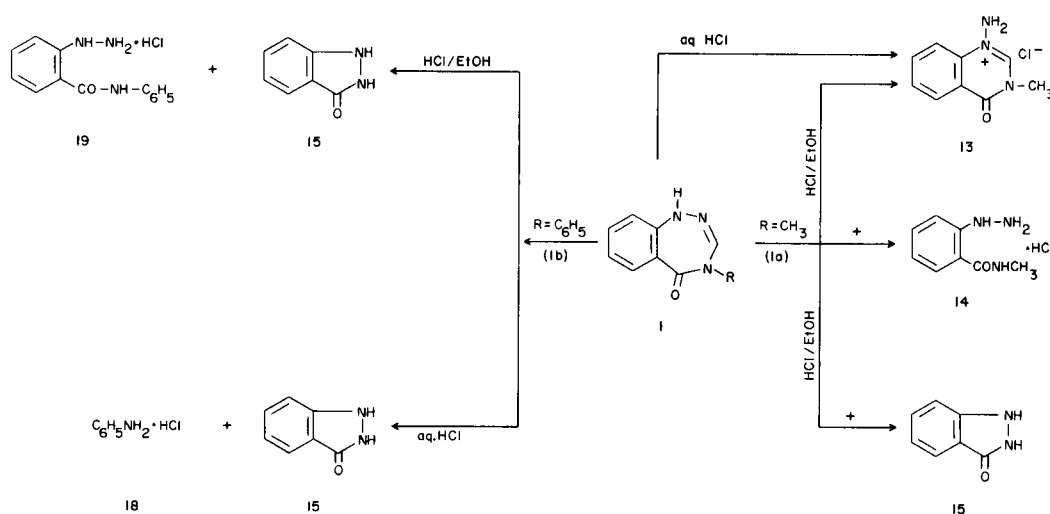


quaternary quinazolone salt through isomerization in acidic aqueous medium was not observed.

These reactions demonstrate the different behavior of the 4-methyl and 4-phenyl derivatives (**1a** and **1b**, respectively), owing probably to different stabilities of their methylated products. On the other hand, the formation of 2-methylindazolone provides evidence that methylation takes place at the nitrogen atom at position 2 in both cases. Furthermore, the isolation of aniline (from **1b**) shows that the formation of 2-methylindazolone **12** occurs *via* amidic nitrogen elimination from position 4. Similar, but not strictly parallel behavior of **1a** and **1b** towards acidic agents was also observed.

Compound **1a** on reaction with aqueous hydrochloric acid or with an anhydrous solution of ethanolic hydrochloric acid underwent an isomerization process which could be explained *via* protonation of the nitrogen atom at position 2. The result was the formation of a product having a dipolar structure, recognized as 1-imino-3-

Chart III



methylquinazolin-4-one **13** (Chart III). In the presence of ethanolic hydrochloric acid, the formation of *o*-hydrazinobenzoic acid methylamide **14** and indazolone **15** was also observed. The identification of **13** was accomplished by catalytic hydrogenation to give 1-amino-3-methyltetrahydroquinazolin-4-one **16** and by comparison of the latter with an authentic sample obtained by reduction of 1-nitroso-3-methyltetrahydroquinazolin-4-one **17**, prepared by nitrosation of 3-methyltetrahydroquinazolin-4-one **10** (Chart V). Compound **1b**, by reaction with the same acidic reagents under the same conditions, did not give any rearrangement products, but rather gave products from a further hydrolytic cleavage, such as indazolone **15** and aniline **18** or *o*-hydrazinobenzoic acid anilide **19** and indazolone **15** (Chart III), depending on reaction conditions. Compound **19** was identified by con-

version into its benzal derivative **20** (Chart V), obtained in turn by condensing *o*-benzalhydrazinobenzoic acid **21** and aniline with dicyclohexylcarbodiimide in tetrahydrofuran.

Chart IV

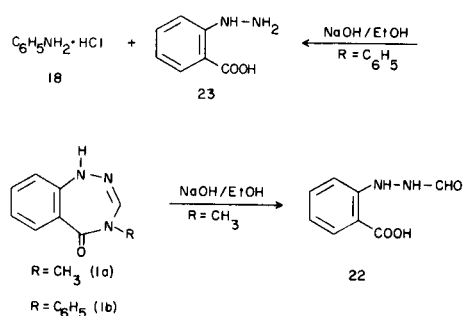
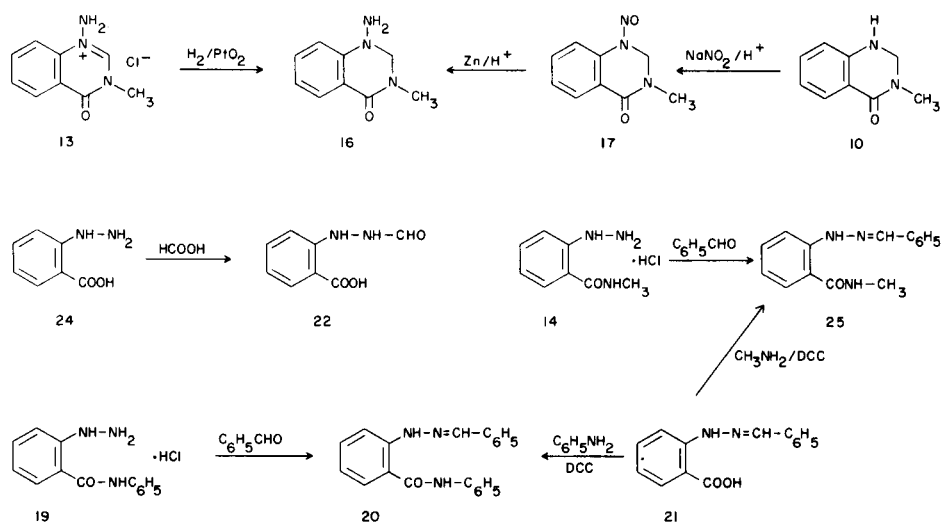


Chart V



Finally, in order to complete the study of the chemical behavior of the 1,2,4-benzotriazepine ring, we submitted **1a** and **1b** to the action of alkaline reagents (Chart IV). This treatment resulted in ring opening and the formation of hydrolytic cleavage products: from **1a**, *N*-formyl-*o*-hydrazinobenzoic acid **22**; and from **1b**, *o*-hydrazinobenzoic acid **23** and aniline were isolated.

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. Ir spectra were recorded in Nujol on a Perkin Elmer model 247 spectrophotometer. Nmr spectra were taken on a Varian A-60A spectrometer (TMS as internal standard, s = singlet, d = doublet, m = multiplet). Tlc were performed with a layer of 250 μ of silica gel GF 254 (purchased from Merck, A. G.) using uv light (254 nm) as developer. The solvent employed is indicated in each single case.

Benzaldehyde Methylphenylhydrazone (10) (**4**).

Method A.

A mixture of benzaldehyde phenylhydrazone **3** (2 g.) and 10 ml. of methyl fluorosulfonate was stirred at room temperature until solution was complete (about 20-30 minutes). The solution was then evaporated to dryness under reduced pressure and the residue was taken up with a little ethanol. The solid which formed was collected by filtration and recrystallized from 95% ethanol, yielding 1.2 g. (57%), m.p. 101-103° [lit. (10) m.p. 102-102.5°], of a compound identical in all respects with the sample prepared from benzaldehyde and methylphenylhydrazine. Method B.

To a stirred solution of benzaldehyde phenylhydrazone **3** (5 g., 25.5 mmoles) in 125 ml. of dry benzene, methyl fluorosulfonate (2.75 g., 24 mmoles) dissolved in 10 ml. of dry benzene was added dropwise at room temperature. The mixture was heated to 60° and stirring was continued for 3 hours. After cooling, the solution was washed with 5% sodium bicarbonate and then with water. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue, containing the reaction product and unreacted material, was purified by chromatography on a silica gel column, eluting with a mixture ethanol-benzene (4:1 by volume). By further recrystallization from 95% ethanol, 1 g. (20%) of **4** was obtained identical to that prepared by Method A.

2,4-Dimethyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepinium Fluorosulfonate (Chart I) (**5**).

To a suspension of 4-methyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine **1a** (5 g., 28.5 mmoles) in 250 ml. of dry benzene, a solution of methyl fluorosulfonate (3.52 g., 31 mmoles) in 25 ml. of dry benzene was dropped in and the mixture was stirred for 1 hour. The solid was then filtered and thoroughly washed with dry benzene (11). The crude product (7.6 g., 91%) was purified by crystallization from water and then from 2-propanol. Compound **5** had m.p. 160-165°; ir: ν max 3300-3200 (NH), 1730 (CO), 1690 (N=C) cm^{-1} ; nmr (DMSO-*d*₆): δ 9.65 (1H, s, CH=), 8.2-7.5 (4H, m, aromatics), 3.68 (3H, s, N-CH₃), 3.38 (1H, s, NH), 2.96 (3H, d, N-CH₃).

Anal. Calcd. for C₉H₉N₃O-CH₃SO₃F: C, 41.53; H, 4.18; N, 14.53. Found: C, 41.90; H, 4.10; N, 14.55.

1-Methylimino-3-methyl-4-oxoquinazolinium Fluorosulfonate (**6**).

Compound **5** (0.5 g.) was refluxed under stirring with 10 ml. of 15% hydrochloric acid for 0.5 hour. After evaporation under reduced pressure, the residue was crystallized from 50% ethanol, yield 0.3 g. (60%), m.p. 206-208°; ir: ν max 3290 (NH), 1725 (CO), 1640 (N=C) cm^{-1} ; nmr (DMSO-*d*₆): δ 9.70 (1H, s, CH=), 8.2-7.9 (4H, m, aromatics), 6.9 (1H, broad, s, NH), 3.70 (3H, s, N-CH₃), 3 (3H, s, NH-CH₃).

Anal. Calcd. for C₉H₉N₃O-CH₃SO₃F: C, 41.53; H, 4.18; N, 14.53. Found: C, 41.72; H, 4.68; N, 14.86.

By treatment of an aqueous suspension of the fluorosulfonate **6** with 5% sodium bicarbonate, 1-methylimino-3-methylquinazolin-4-one **7** was formed, insoluble in all common organic solvents, m.p. 290-296°.

Anal. Calcd. for C₁₀H₁₁N₃O: C, 63.45; H, 5.86; N, 22.21. Found: C, 63.35; H, 5.86; N, 22.20.

Reactions of 2,4-Dimethyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepinium Fluorosulfonate **5** with Alkalies (Chart I).

A) With Sodium Bicarbonate.

A suspension of **5** (2 g.) in a small amount of water was treated at room temperature for 10 minutes with an aqueous solution of 5% sodium bicarbonate. The mixture was repeatedly extracted with chloroform and the combined extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue which was taken up with a mixture of hexane-ethanol (3:1 by volume). When kept overnight in a refrigerator, a solid product was formed, which was further purified by crystallization from hexane-ethanol, furnishing 0.8 g. (38.6%) of *N*-methyl-*N*-formyl-*o*-hydrazinobenzoic acid methylamide **11**, m.p. 125-127° ir: ν max 3340 (NH), 2795 (CH, formyl group), 1680, 1640, (CO) cm^{-1} ; nmr (deuteriochloroform): δ 8.11 (1H, s, CHO), 7.8-7.1 (4H, m, aromatics), 6.8 (1H, broad, s, NH), 5.4 (1H, broad, s, NH), 2.81 (3H, d, N-CH₃), 2.53 (3H, d, N-CH₃).

Anal. Calcd. for C₁₀H₁₃N₃O₂: C, 57.91; H, 6.32; N, 20.26. Found: C, 57.85; H, 6.43; N, 20.16.

By warming in ethanol containing a few ml. of 30% sodium hydroxide, 2-methylindazolone **12** was formed (m.p. 190-195° dec) (**12**).

B) With Sodium Hydroxide.

Compound **5** (1.5 g.) in 20 ml. of 95% ethanol and 30 ml. of 15% sodium hydroxide was heated at 50° for 3 hours under stirring. The reaction mixture was then distilled, collecting a small amount of ethanol, and the residual solution was evaporated to dryness *in vacuo*. The distillate treated with an ethanolic solution of picric acid gave a precipitate of methylamine picrate, m.p. 209-211° [lit. (13) m.p. 215°]. The residue of distillation after crystallization from 95% ethanol yielded a product with m.p. 189-192° dec, which was recognized from elemental data, physico-chemical properties and by comparison of the ir spectrum with an authentic sample, as 2-methylindazolone **12** [lit. (12) m.p. 192-200° dec]; ir: ν max 3050 (NH), 1640, 1620 (CO) cm^{-1} .

Anal. Calcd. for C₈H₈N₂O: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.63; H, 5.31; N, 19.00.

Catalytic Hydrogenation of 2,4-Dimethyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepinium Fluorosulfonate (**5**) (Chart I).

Compound **5** (4 g.) in 250 ml. of dry ethanol was hydrogenated at room temperature and atmospheric pressure over platinum oxide (0.4 g.). After filtering off the catalyst and removing the solvent, the residue (2.5 g.) was taken up with an aqueous solution of potassium carbonate, extracted with ethyl ether and evaporated to dryness, giving an oily product which solidified when cooled. After crystallization from isopropanol, 0.8 g. (30%) of 1-methylamino-3-methyltetrahydroquinazolin-4-one **8** was obtained, m.p. 60-61°; ir: ν max 3245 (NH), 1635 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 8-6.7 (4H, m, aromatics), 4.45 (2H, s, CH₂), 3.3 (1H, broad, s, NH), 3.05 (3H, s, NCH₃), 2.70 (3H, s, NH-CH₃).

Anal. Calcd. for C₁₀H₁₃N₃O: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.72; H, 6.68; N, 22.35.

Reduction of 1-Methylimino-3-methyl-4-oxoquinazolinium Fluorosulfonate (**6**) (Chart I).

A) With Sodium Borohydride.

To a stirred solution of **6** (1 g., 3.45 mmoles) in 30 ml. of 50% ethanol, sodium borohydride (0.2 g., 5.3 mmoles) was added portionwise. Stirring was continued for 1 hour at room temperature, and the solution then concentrated under reduced pressure to a small volume. The residual solution saturated with solid potassium carbonate and extracted with ethyl ether, furnished, after removal of the solvent, an oily residue, which by

ice-cooling yielded a solid product with m.p. 60-61° (from 2-propanol). The product was recognized as 1-methylamino-3-methyltetrahydroquinazolin-4-one **8** by comparison of ir and nmr spectra with the sample obtained by catalytic hydrogenation from **5**.

B) With Hydrogen over Platinum Oxide.

A suspension of **6** (2.5 g.) in 150 ml. of 95% ethanol was hydrogenated at room temperature and atmospheric pressure over platinum oxide (0.25 g.). When the hydrogen absorption ceased, the catalyst was filtered off and the solvent was removed under reduced pressure. The very hygroscopic residue was taken up with an aqueous solution of 5% sodium bicarbonate and extracted with ethyl ether. The oily residue (2.1 g.) obtained after removal of solvent was purified by ball tube distillation at 90-110°/0.5 mm. The solid product formed by cooling melted at 104-105° and was recognized as 3-methyl-4-quinazolone **9**, by comparison of the ir spectrum with an authentic sample [lit. (14) m.p. 105°]. An attempted hydrogenation of 1-methylimino-3-methyl-4-quinazolone **7** under the same reaction conditions was unsuccessful.

C) With Hydrogen over Palladium on Carbon.

A suspension of **6** (2 g.) in 100 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon. When the hydrogen absorption ceased, the catalyst was filtered off and the solvent was removed under reduced pressure. The residue was taken up with an aqueous solution of 5% sodium bicarbonate, extracted with chloroform, and the solvent was evaporated. The oily residue was treated with ethanol-ethyl ether (1:1 by volume) and crystallized from benzene, affording 0.5 g. of 3-methyltetrahydroquinazolin-4-one **10**, m.p. 109-111° [lit. (14) m.p. 111-113°], identical in all respects to an authentic sample.

Reaction of 4-Phenyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine (**1b**) with Methyl Fluorosulfonate (Chart II).

To a stirred solution of 4-phenyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine **1b** (1.5 g., 6.32 mmoles) in 60 ml. of dry benzene, methyl fluorosulfonate (0.865 g., 7.58 mmoles) dissolved in 5 ml. of dry benzene was added dropwise at room temperature. The stirring was continued for 2 hours. The resulting precipitate was then filtered and thoroughly washed with the same solvent.

The solid obtained (1.5 g.), examined by tlc (benzene/ethyl acetate 1:1 by volume as eluent), showed three marked spots and several by-products. This mixture was suspended in 25 ml. of water, refluxed for 1 hour, and then distilled. The distillate in which formic acid was detected through its specific reactions (reduction of Tollens' reagent, brown precipitate with silver nitrate, white precipitate with mercuric chloride solution) (**15**) was collected.

After distillation, the dry residue was taken up with absolute ethanol and filtered, furnishing aniline fluorosulfonate (m.p. > 290°), identified by comparison of the ir spectrum with an authentic sample. The ethanolic mother liquor was evaporated to dryness under reduced pressure, and the solid residue was taken up with 5% sodium bicarbonate solution. Filtration afforded 2-methylindazolone **12**, m.p. 195-200° dec, identical in all respects to an authentic sample.

Reaction of 4-Methyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine (**1a**) with Acids (Chart III).

A) With Anhydrous Ethanolic Hydrochloric Acid.

To a stirred solution of **1a** (2 g., 11.4 mmoles) in 70 ml. of dry benzene, 14 ml. of a 9% solution anhydrous hydrochloric acid in absolute ethanol (34.2 mmoles) was added. After 2 hours of stirring, the resulting precipitate was collected by filtration affording 1.3 g. of *o*-hydrazinobenzoic acid methylamide hydrochloride **14**, m.p. 132° dec (from ethanol-ethyl ether) (**16**). The product reduces Fehling's and Tollens' reagents.

Anal. Calcd. for C₉H₁₁N₃O·HCl: C, 47.65; H, 5.99; N, 20.84. Found: C, 47.60; H, 5.97; N, 20.79.

The corresponding benzal derivative (**17**), m.p. 125-127° (from absolute ethanol), was identical in all respects to that prepared in-

dependently (see **25** Chart V).

By evaporating the filtrate of the reaction mixture under reduced pressure at room temperature, about 1 g. of residue was obtained, which examined by tlc (benzene/ethyl acetate/acetic acid 4:5:1 by volume as eluent), showed two spots. An aliquot of the mixture, after crystallization from water and then from absolute ethanol, gave the indazolone **15**, m.p. 244-246°, recognized by comparison with an authentic sample (**18**). Another aliquot taken up with water and made alkaline with sodium bicarbonate gave 1-imino-3-methylquinazolin-4-one **13**, m.p. 261° dec (from acetic acid-absolute ethanol). Compound **13** is insoluble in water and in common organic solvents. It reduces Fehling's and Tollens' reagents; ir: ν max 3230 (NH), 1650 (CO) cm⁻¹.

Anal. Calcd. for C₉H₉N₃O: C, 61.70; H, 5.18; N, 22.99. Found: C, 61.45; H, 4.98; N, 23.04.

The hydrochloride of **13** had m.p. 226-228° (from absolute ethanol).

Anal. Calcd. for C₉H₉N₃O·HCl: C, 51.07; H, 4.76; N, 19.85. Found: C, 51.46; H, 4.88 N, 20.08.

B) With Aqueous 2*N* Hydrochloric Acid.

Compound **1a** (10 g.) in 50 ml. of 95% ethanol and 150 ml. of 2*N* hydrochloric acid was heated under reflux for 2 hours. After evaporation of the solvent under reduced pressure, the residue, examined by tlc (benzene/ethyl acetate/acetic acid 4:5:1 by volume as eluent), proved to be a mixture of **13** and **15** (the former in a major amount). By crystallization from 95% ethanol, 7.4 g. (61%) of 1-imino-3-methylquinazolin-4-one hydrochloride **13**. HCl, practically in a pure state, were obtained, m.p. 228°. The mixed m.p. with the sample isolated by the Method A was unaltered and the ir spectra were identical.

Reactions of 4-Phenyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine (**1b**) with Acids (Chart II).

A) With Anhydrous Ethanolic Hydrochloric Acid.

To a stirred solution of **1b** (2 g., 8.37 mmoles) in 65 ml. of dry benzene, 7.4 ml. of 12.5% solution of anhydrous hydrochloric acid in absolute ethanol (25.5 mmoles) was added at room temperature. Stirring was continued for 2 hours. The resultant precipitate was collected by filtration and was identified as a mixture (m.p. 134° dec) of *o*-hydrazinobenzoic acid anilide hydrochloride **19** (as a major part) and of indazolone **15**. An aliquot of this mixture (0.3 g.), dissolved in 10 ml. of water containing sodium acetate (0.09 g., 1.11 mmoles) was treated with benzaldehyde (0.116 g., 1.1 mmoles) by warming at 50° for 30 minutes, affording 0.3 g. of the benzal derivative **20** (Chart V), m.p. 191-193° (from absolute ethanol). The product was unaltered by mixed m.p. with a sample prepared independently. The benzene mother liquors were evaporated to dryness and the residue was crystallized from ethanol, affording indazolone **15**, m.p. 245-247°, identified by comparison with an authentic sample (**18**).

B) With Aqueous 2*N* Hydrochloric Acid.

Compound **1b** (2 g.) in 10 ml. of 95% ethanol and 30 ml. of 2*N* hydrochloric acid was heated under reflux for 2 hours. The solvent was removed under reduced pressure, and the residue was crystallized from ethanol-dry ethyl ether, yielding 0.6 g. of aniline hydrochloride **18**, m.p. 192-194°. The mother liquors were evaporated to dryness. The oily residue taken up with water solidified and by crystallization from absolute ethanol it gave 0.6 g. of indazolone **15**, m.p. 245-247° unaltered by a mixed m.p. with an authentic sample (**18**).

Reaction of 4-Methyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine (**1a**) with Alkali (Chart IV).

Compound **1a** (1 g.) dissolved in 5 ml. of 95% ethanol and 15 ml. of 2*N* sodium hydroxide was heated at 50° for 2 hours. After cooling, the solution was acidified with 2*N* hydrochloric acid. The resultant precipitate was collected by filtration and crystallized from absolute ethanol, furnishing *N*-formyl-*o*-hydrazinobenzoic acid **22**, m.p. 218°, unaltered by mixed m.p. with the sample prepared independently.

Reaction of 4-Phenyl-5-oxo-1*H*-4,5-dihydro-1,2,4-benzotriazepine (**1b**) with Alkali (Chart IV).

A solution of **1b** (3 g.) in 15 ml. 95% ethanol and 45 ml. of 2*N* sodium hydroxide was refluxed for 2 hours. The mixture was then steam distilled; the distillate (about 500 ml.) was acidified with hydrochloric acid and evaporated to dryness. Thus 1.7 g. of aniline hydrochloride **18** was obtained, m.p. 192-194°, unaltered by mixed m.p. with an authentic sample. The remaining solution was concentrated to a small volume and acidified with concentrated hydrochloric acid. Thus, 1.2 g. of *o*-hydrazinobenzoic acid hydrochloride **23** was obtained, m.p. 196° dec, identical in every respect with an authentic sample (**18**).

1-Nitroso-3-methyltetrahydroquinazolin-4-one (**17**) (Chart V).

To a solution of sodium nitrite (0.214 g., 3.1 mmoles) in 30 ml. of water, 3-methyltetrahydroquinazolin-4-one (**14**) **10** (0.5 g., 3.1 mmoles) dissolved in 60 ml. of 1*N* hydrochloric acid was added dropwise at 4-8°. The precipitate which formed was collected by filtration, washed with water and crystallized from chloroform-isopropyl ether, yielding 0.3 g. (60%) of pure **17**, m.p. 115-116°.

Anal. Calcd. for C₉H₁₁N₃O₂: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.22; H, 4.56; N, 21.78.

1-Amino-3-methyltetrahydroquinazolin-4-one (**16**) (Chart V).

Method A: from **17**.

To a solution of **17** (1 g., 5.2 mmoles) in 50 ml. of 50% methanol, zinc powder (1.3 g., 20 m-atom) was added. Then, 1.7 ml. of glacial acetic acid was added dropwise at room temperature and the mixture was heated to 50-60° for 2-3 hours. After cooling, the mixture was made alkaline with 2*N* sodium hydroxide and extracted with chloroform. The organic layer was separated, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallized from 95% ethanol. Yield 0.4 g. (40%), m.p. 121-123°. The product is sparingly soluble in water and reduces the Tollens', but not the Fehling's reagent.

Anal. Calcd. for C₉H₁₁N₃O: C, 61.01; H, 6.21; N, 23.73. Found: C, 61.10; H, 5.96; N, 23.54.

Method B: from **13**-HCl.

A solution of **13**-HCl (1 g.) in 70 ml. of 95% ethanol was hydrogenated at room temperature and atmospheric pressure over platinum oxide (100 mg). When the hydrogen absorption ceased, the catalyst was filtered off, the solvent was removed under reduced pressure and the residue taken up with potassium carbonate solution. It was then extracted with chloroform and evaporated to dryness, affording after crystallization from ethanol, 0.8 g. (94%) of **16**, m.p. 120-121°, unaltered by mixed m.p. with the sample obtained by Method A.

o-Benzalhydrazinobenzoic Acid Anilide (**20**) (Chart V).

To a stirred mixture of *o*-benzalhydrazinobenzoic acid (**18**) **21** (1.5 g., 6.2 mmoles) and aniline (0.58 g., 6.2 mmoles) in 15 ml. of dry tetrahydrofuran, dicyclohexylcarbodiimide (1.94 g., 6.3 mmoles) in 5 ml. of tetrahydrofuran was added portionwise. The stirring was continued for 2 hours at room temperature and the dicyclohexylurea formed which was filtered off. The solvent was removed and the residue crystallized from absolute ethanol, yielding 0.7 g. of pure **20**, m.p. 192-193°.

Anal. Calcd. for C₂₀H₁₇N₃O: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.12; H, 5.33; N, 13.41.

N-Formyl-*o*-hydrazinobenzoic Acid (**22**) (Chart V).

A mixture of *o*-hydrazinobenzoic acid (**18**) **24** (1.5 g., 10 mmoles) in 20 ml. of 90% formic acid was heated under reflux for 45 minutes. The mixture was then evaporated to dryness under reduced pressure and the residue crystallized from ethanol, yield 0.7 g., m.p. 218°.

Anal. Calcd. for C₉H₈N₂O₃: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.42; H, 4.45; N, 15.61.

o-Benzalhydrazinobenzoic Acid Methylamide (**25**) (Chart V).

A mixture of *o*-benzalhydrazinobenzoic acid (**18**) **21** (3 g., 12.4 mmoles), anhydrous methylamine (5 ml.), dicyclohexylcarbodiimide (3.98 g., 12.6 mmoles) in 35 ml. of dry tetrahydrofuran was placed in a sealed tube and kept overnight at room temperature. The dicyclohexylurea which formed was then filtered off, the solvent removed under reduced pressure and the residue chromatographed on a silica gel column, eluting with a mixture of ethyl acetate/benzene (4:1 by volume). The isolated product was purified by further crystallization from anhydrous ethyl ether, yield 0.50 g., m.p. 124-126°.

Anal. Calcd. for C₁₃H₁₃N₃O: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.89; H, 5.82; N, 16.65.

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REFERENCES AND NOTES

- (1) Sixth paper in the series: Studies on 7-Membered Benzo Condensed Heterocycles. For the preceding papers see reference 2.
- (2) M. Bianchi, A. Butti, S. Rossi, F. Barzaghi and V. Marcaraia, *Eur. J. Med. Chem.*, **12**, 263 (1977).
- (3) V. Franzen and H. E. Driesen, *Chem. Ber.*, **96**, 1881 (1963).
- (4) H. König, H. Metzger and K. Seelert, *ibid.*, **98**, 3724 (1965).
- (5) W. G. Kenyon and C. R. Hauser, *J. Org. Chem.*, **30**, 292 (1965).
- (6) A. Jonczyk, J. Wlostowska and M. Makosza, *Synthesis*, 795 (1976).
- (7) A similar example of this kind of rearrangement was found also in the 1,2,5-benzotriazepine series (**8**) and more recently R. W. Leiby and N. D. Heindel (**9**) described a basic-induced ring contraction of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones to 3-methylamino-4(3*H*)-quinazolinones.
- (8) S. Rossi, O. Pirola and F. Selva, *Tetrahedron*, **24**, 6395 (1968).
- (9) R. W. Leiby and N. D. Heindel, *J. Org. Chem.*, **42**, 161 (1977).
- (10) A. Elbers, *Ann. Chem.*, **227**, 340 (1885).
- (11) By standing in the open air, the crude product quantitatively was transformed into 1-methylimino-3-methyl-4-oxoquinazolinium fluoro-sulfonate **6**.
- (12) J. Schmutz, F. Hunzicker and W. Michaelis, *Helv. Chim. Acta*, **47**, 1986 (1964).
- (13) A. J. Vogel, "Practical Organic Chemistry", 3rd Ed., Longman Group Limited, London, 1956, p. 424.
- (14) J. Maillard, M. Bénard, M. Vincent, Vo-Van-Tri, R. Jolly, R. Morin, C. Menillet and Mrs. Benharkate, *Chim. Ther.*, **2**, 202 (1967).
- (15) H. Persiel, in "Houben Weyl's Methoden der Organischen Chemie", 4th Ed., Vol. 2, Georg Thieme Verlag, Stuttgart, West Germany, 1953, pp. 944, 980.
- (16) At the Kofler apparatus, the product melts at 133° and then solidifies in a modified crystalline form and again melts at 189-190°.
- (17) This compound was prepared from **14**-HCl (0.5 g., 2.5 mmoles), sodium acetate (0.2 g., 2.5 mmoles) and benzaldehyde (0.265 g., 2.5 mmoles), by warming in 15 ml. of water at 50° for 30 minutes, yield 70%. It did not reduce Fehling's and Tollens' reagents.
- (18) E. F. M. Stephenson, in "Organic Synthesis", Coll. Vol. III, E. C. Horning Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 475.