# Synthesis of Novel Spiro Heterocycles. 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes[1]

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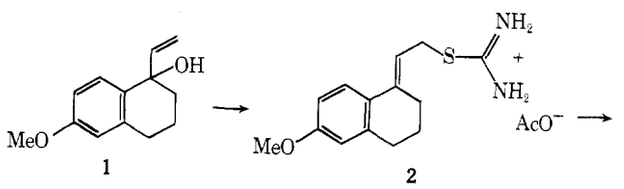
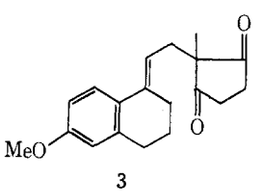
Reaction of the vinyl 4-hydroxyalkyl ketones **4a–d** with thiourea in acetic acid gave epimeric mixtures of the 8-substituted 2-amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes **15a–d** (major) and **16a–d** (minor). The relative stereochemistry of these epimers was deduced using nmr spectroscopy. These adducts were selectively monoacylated in series **a–c**, giving the derivatives **17** and **18**. The unsubstituted amino spirothiazinepyran **24** was prepared by treatment of the Mannich base **23** or the diol **31e** with thiourea. An X-ray crystal structure determination of the *p*-bromobenzoyl derivative **35** confirmed the structures of these novel heterocycles. These compounds exhibit facile ring–open-chain isomerism under acidic conditions, certain manifestations of which are described. Reaction of the aminothiazine mixtures **15b, 16b** and **15d, 16d** with 2-methyl-1,3-cyclopentanedione in the presence of aqueous acid led, in modest yields, to the dienes **8b** and **8d**, respectively. The latter compounds have previously been shown to be useful in certain total syntheses of 19-norsteroids and related compounds.

The allylic isothiuronium salt **2** was first synthesized by Kuo, Taub, and Wendler[2] and shown to be of utility in a variation of the Torgov–Smith[3-5] estrone total synthesis. This material is produced in high yield by treatment of the conventional intermediate,[3-5] vinyl carbinol **1**, with thiourea in acetic acid and couples efficiently with 2-methyl-1,3-cyclopentanedione giving the dione **3**. Related isothiuronium salts have been prepared and used as intermediates for the synthesis of thiasteroids,[6] oxasteroids,[7] and steroid analogs.[8]



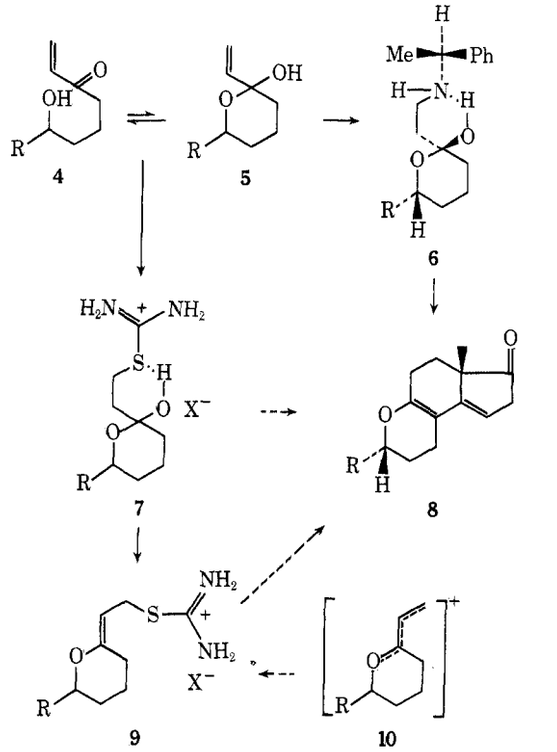
**1** **2**



**3**

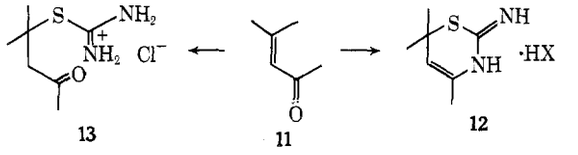
In our own laboratories, several efficient schemes for the total synthesis of optically active 19-norsteroids have been developed which utilize vinyl 4-hydroxyalkyl ketones such as **4** as key intermediates.[9] Addition of optically active α-methylbenzylamine to these vinyl ketones gives a mixture of diastereomeric Mannich bases which can be separated by recrystallization of the oxalic acid salts.[10] The resultant diastereomer **6** (or related derivatives) on condensation with 2-methyl-1,3-cyclopentanedione then yields the key steroidal precursor, dienol ether **8**, with substantial asymmetric induction at $C_{13}$ being observed.

The vinyl ketones **4** exist in equilibrium with the hemiketal form **5**, a species which bears a structural resemblance to the carbinol **1**. For this reason we felt that a study of the reaction of thiourea with compounds such as **4** would be of interest in determining whether novel intermediates, capable of optical resolution and useful for the total synthesis of 19-norsteroids (by facile conversion into the dienes **8**), could be produced. We envisioned, for example, formation of the adduct **7**, an intermediate which potentially fulfills these requirements and which possesses structural features in common with both the Mannich bases **6** and the isothiuronium salt **2**. The salt **7** could arise from vinyl ketone **4** *via* conjugate addition of thiourea. Alternatively, the enol ether **9**, another potentially useful intermediate, could be formed under acidic conditions either by dehydration of **7** or from the hemiketal **5** *via* coupling of thiourea with the resonance-stabilized carbocationic species **10**.[11]



**4** **5** **6** **7** **8** **9** **10**

The reaction of thiourea with simple, α,β-unsaturated ketones has been studied.[12-16] The products are generally those derived from conjugate addition of the sulfur atom to the double bond of the enone followed by cyclodehydration. Mesityl oxide (**11**), for example, was reported to give the 2-imino-2,3-dihydro-6*H*-1,3-thiazine salt **12** on treatment with thiourea in the presence of mineral acid.[13-15]



**13** **11** **12**

**Table I**[a]
**8-Substituted 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes**

| Compd | Yield, %[b] | Mp, °C | Crystd from[c] | Ir, cm$^{-1}$ [d] | Nmr[e] $NH_2$[f] | Nmr[e] $C_8H$ | Formula[k] |
|---|---|---|---|---|---|---|---|
| **15a** | 71(74) | Oil[a] | | 3500, 3400, 1630, 1620, 1580 | 4.55 | 4.13[h] | $C_9H_{16}N_2OS$ |
| **16a** | | 144–145 | B–A | 3500, 3400, 1650, 1625, 1580 | 4.67 | 3.67[h] | |
| **15c** | 74(75) | 102–103 | B–H | 3500, 3400, 1630, 1580 | 4.50 | 5.07[i,j] | $C_{14}H_{18}N_2OS$ |
| **16c** | | 166–167 | A | 3500, 3400, 1670, 1650, 1610 | 6.00[g] | 4.60[i] | |
| **15d** | 79 | 126–127 | A | 3500, 3400, 1640, 1580 | 4.58 | 3.85[h] | $C_{15}H_{23}N_3O_2S$ |
| **16d** | | 153–154 | B–H | 3500, 3400, 1640, 1620, 1580 | 4.39 | 3.50[h] | |

[a] Elemental analyses (C, H, N, S) for all compounds except **15a** were submitted to the reviewers and found to be within acceptable limits. Compound **15a** was analyzed as the maleate salt, which is described in the experimental section. [b] Based on lactones **14**. The figures in parentheses are the yields starting from the Mannich bases **26a** and **26c**. [c] B = benzene, A = acetonitrile, H = hexane. Colorless solids were obtained. [d] $NH_2$ and C=N absorptions measured in $CHCl_3$ solution. [e] Measured in $CDCl_3$ solution (unless otherwise noted) with TMS as an internal standard. Chemical shifts ($\delta$) reported in parts per million. [f] Two-proton singlet resonances except for **16c**. [g] Broad envelope measured in DMSO-$d_6$. [h] One-proton multiplet ($CDCl_3$). [i] Broadened, one-proton doublet, $J$ = 10 Hz (DMSO-$d_6$). [j] One-proton doublet of doublets, $J$ = 2, 12 Hz, centered at $\delta$ 5.11 in $CDCl_3$. [k] All compounds gave molecular ions in the low-resolution mass spectra corresponding to these molecular formulas. M − 28 peaks[22] were exhibited by all compounds except **15c**.

Willems and Vandenberghe,[16] on the other hand, claimed that interaction of **11** with isothiuronium chloride produced the open-chain isothiuronium salt **13**.

## Results

Our initial studies were carried out utilizing the readily available, racemic, monosubstituted $\delta$-lactones **14a**,[17] **14b**,[18] **14c**,[19] and **14d**[20] (Scheme I) as starting materials. These compounds were treated with vinylmagnesium chloride at −50 to −60°[21] giving the vinyl ketones **4a–d**. The latter intermediates, without purification, were treated with thiourea in glacial acetic acid at room temperature,[2] producing, in each series, not the desired adducts **7** or **9** but rather mixtures of two isomeric spirocyclic products **15a–d** and **16a–d** in overall yields of 63–79% based on starting lactone. The epimers **15** and **16** were readily distinguished using thin layer chromatography, the major epimer **15** (see below) being the more mobile component. Separation of these mixtures was difficult but could be accomplished in series **a**, **c**, and **d** using a combination of dry-column chromatography and recrystallization.

Assignment of the novel spirothiazinepyran structures **15** and **16** to the adducts rests on the following data. These compounds were all found to be strong bases which on the basis of microanalytical and mass spectral data were derived from addition of thiourea to the vinyl ketones **4** followed by loss of a molecule of water. The infrared spectra showed strong bands in the $NH_2$ and C=N regions consistent with the presence of an aminothiazine ring. Resonance peaks near 4.5 ppm in the pmr spectra also indicated the presence of the $NH_2$ group. The ultraviolet spectra exhibited no absorption above 205 nm except that due to the chromophores in the substituents R (**c** and **d** series). The mass spectra of the adducts generally showed M − 28 peaks corresponding to loss of ethylene from the thiazine ring *via* a retro Diels–Alder process. This mode of fragmentation is characteristic of 2-amino-5,6-dihydro-4*H*-1,3-thiazines.[22]

A comparison of the pmr spectra of each pair of adducts revealed that, in every series, the resonance due to the axial $C_8$ proton (H–C–O) of the major epimer occurred at lower field than the corresponding resonance arising from the minor epimer. Treatment of the thiazine mixtures in series **a–c** with acetic anhydride–pyridine gave the corresponding mixtures of acetyl derivatives **17** and **18** (R′ = $CH_3$; uv max 260–265 nm, see below) which, in contrast to the parent amines, could be readily separated by chromatography on silica gel. As in the case of the parent thiazines, the resonance band due to the $C_8$ proton in the pmr spectrum of the major acyl derivative was detected at lower field than that due to the minor epimer. These data are summarized in Tables I and II. By integration of the *N*-acetyl peak areas due to **17c** and **18c** in the crude mixture, it was possible to estimate that the ratio of parent amines was approximately 3:1.

It would be expected that the epimer in which the $C_8$ proton encounters a 1,3-diaxial interaction with the nitro-

**Scheme I**

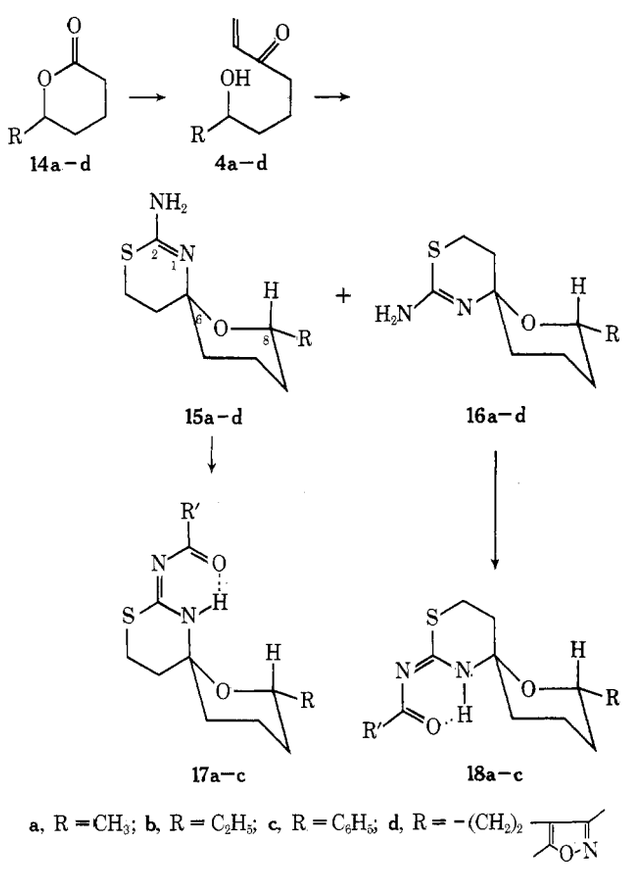


**Table II**[a]
**2-Acylimino-7-oxa-3-thia-1-azaspiro[5.5]undecanes**

| Compd | R′ | Mp, °C | Crystd from[b] | Uv max (ε) 95% EtOH; 0.1 *N* HCl | Ir, $cm^{-1}$ [c] | Nmr[e] $C_4$ H | | $C_8$ H | Formula[n] |
|---|---|---|---|---|---|---|---|---|---|
| **17a** | $CH_3$ | 113–114.5 | H | 220 (6250), 238 (6650), 266 (13,800); 225 (11,000), 245 (11,800) | 3400–3100, 1700 (w), 1595, 1550 | 3.53[f] | 2.72[g] | 3.78[h] | $C_{11}H_{18}N_2O_2S$ |
| **18a** | $CH_3$ | 106–107 | H–B | 222 (6650), 239 (7150), 264 (14,020); 223 (11,000), 245 (12,180) | 3400–3100, 1710 (w), 1600, 1550 | 3.19[i] | 2.67[j] | 3.61[h] | |
| **17b** | $CH_3$ | 79–80 | H–B | 222 (7250), 238 (7380), 265 (15,900); 225 (11,350), 246 (12,600) | 3400–3100, 1700 (w), 1595, 1550 | 3.54[f] | 2.72[g] | 3.54[h] | $C_{12}H_{20}N_2O_2S$ |
| **18b** | $CH_3$ | 98–99 | H–B | 223 (6450), 243 (7150), 265 (14,950); 224 (11,100), 247 (12,000) | 3400–3100, 1595, 1555 | 3.24[i] | 2.68[j] | 3.33[h] | |
| **17c** | $CH_3$ | Oil | | 208 (13,980), 235 (7250), 262 (11,650); 224 (11,500), 244 (12,200) | 3400–3100, 1700 (w), 1595, 1550 | 3.51[f] | 2.75[g] | 4.76[k] | $C_{16}H_{20}N_2O_2S$ |
| **18c** | $CH_3$ | 144–145 | H–B | 210 (10,500), 240 (7300), 264 (14,250); 226 (11,500), 245 (12,120) | 3400–3100, 1710 (w), 1600, 1550 | 3.21[i] | 2.77[j] | 4.56[l] | |
| **17c** | *p*-$C_6H_4Br$ | 126.5–127.5 | E | 258 (15,200), 296 (29,600); 268 (26,350) | 1590, 1550[d] | 3.62[f] | 2.72[g] | 4.73[k] | $C_{21}H_{21}BrN_2O_2S$ |
| **18c** | *p*-$C_6H_4Br$ | 157–157.5 | E | 256 (16,100), 295 (29,600); 267 (26,350) | 1595, 1555[d] | 3.27[i] | 2.77[j] | 4.47[l] | |
| **35** | *p*-$C_6H_4Br$ | 128.5–129 | H–B or E | 257 (15,100), 295 (30,200); 220 (10,600), 267 (27,000) | 1595, 1555[d] | 3.62[f] | 2.79[g] | 3.73[m] | $C_{15}H_{17}BrN_2O_2S$ |
| **36** | *p*-$C_6H_4F$ | 150.5–151.5 | H–B or E | 249 (11,200), 290 (26,300); 213 (8840), 258 (23,600) | 1595, 1555[d] | 3.67[f] | 2.83[g] | 3.83[m] | $C_{15}H_{17}FN_2O_2S$ |

[a] Elemental analyses (C, H, N, S) for all compounds were submitted to the reviewers and found to be within acceptable limits. [b] B = benzene, E = ethanol, H = hexane. Colorless solids were obtained. [c] Bands due to NH (broad H-bonded), C=N, and C=O functions ($CHCl_3$). [d] NH bands not detectable in 3% $CHCl_3$ solution but could be detected in KBr disk spectra. [e] Measured in $CDCl_3$ solution with TMS as an internal standard. Chemical shifts (δ) reported in parts per million. [f] One-proton doublet of triplets, $J$ = 4, 12 Hz, axial $C_4$ H. [g] One-proton doublet of triplets, $J$ = 4, 12 Hz, equatorial $C_4$ H. [h] One-proton multiplet. [i] One-proton multiplet approximating a doublet of triplets with average $J$ = 3, 13 Hz. [j] Two-proton multiplet including one of $C_5$ protons. [k] One-proton doublet of doublets, $J$ = 2, 12 Hz. [l] One-proton, broadened doublet, $J$ = 10 Hz. [m] Two-proton multiplet. [n] All compounds gave molecular ions in the low-resolution mass spectra corresponding to these molecular formulas. M − 28 peaks[22] were exhibited by all compounds except **17b** and **17c** (R′ = $CH_3$).

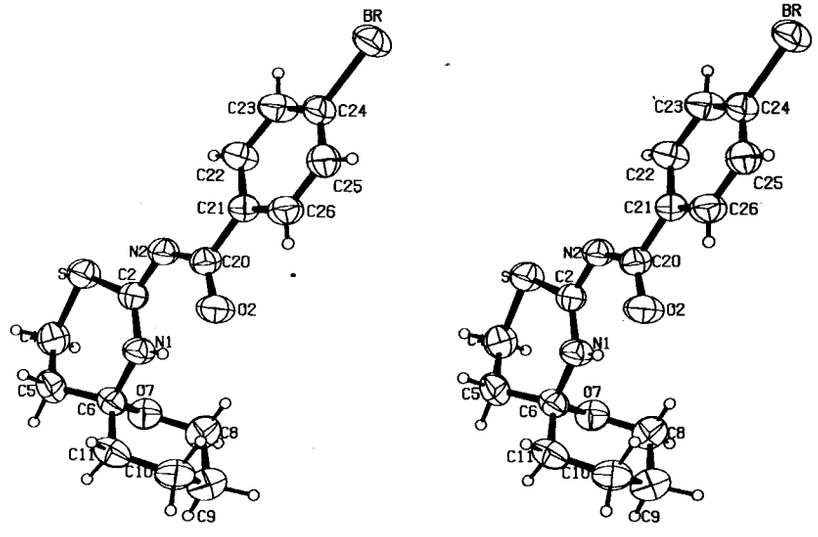
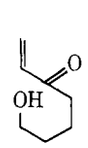


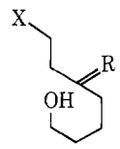

**Figure 1.** Stereoview of **35**.

gen atom of the thiazine ring and is thus more strongly deshielded would exhibit the relatively lower field $C_8$-H resonance.[23] Therefore, we have assigned structure **15** to the major epimer and **16** to the minor epimer in each series. This assignment is consistent with the anomeric effect,[24] on the basis of which it would be predicted that epimer **15**, in which both heteroatoms attached to the spiro center can assume an axial conformation, should predominate.

In order to synthesize the parent aminothiazine in this series, the vinyl ketone **19** or an appropriately disguised derivative such as **20** (which can easily generate **19**) was



**19**

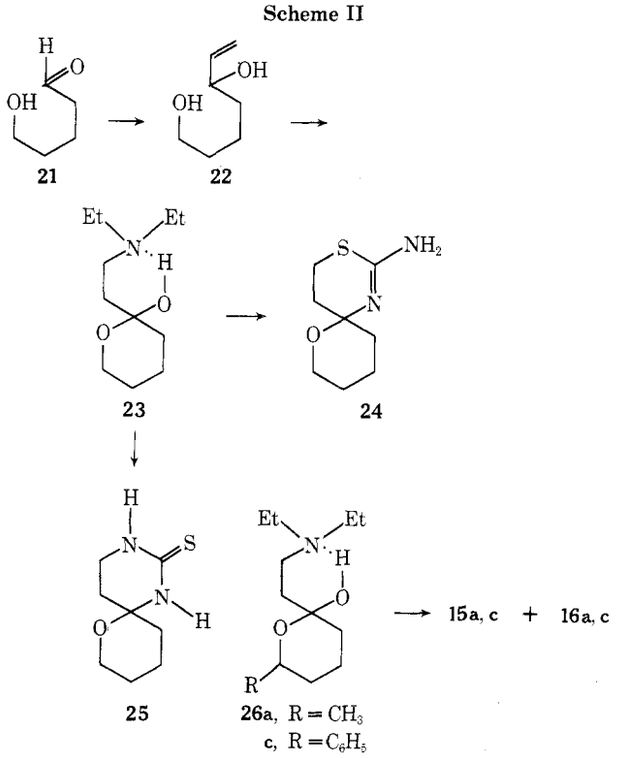


**20**, X = $NEt_2$, OH, halogen, etc.
R = O, $-OCH_2CH_2O-$

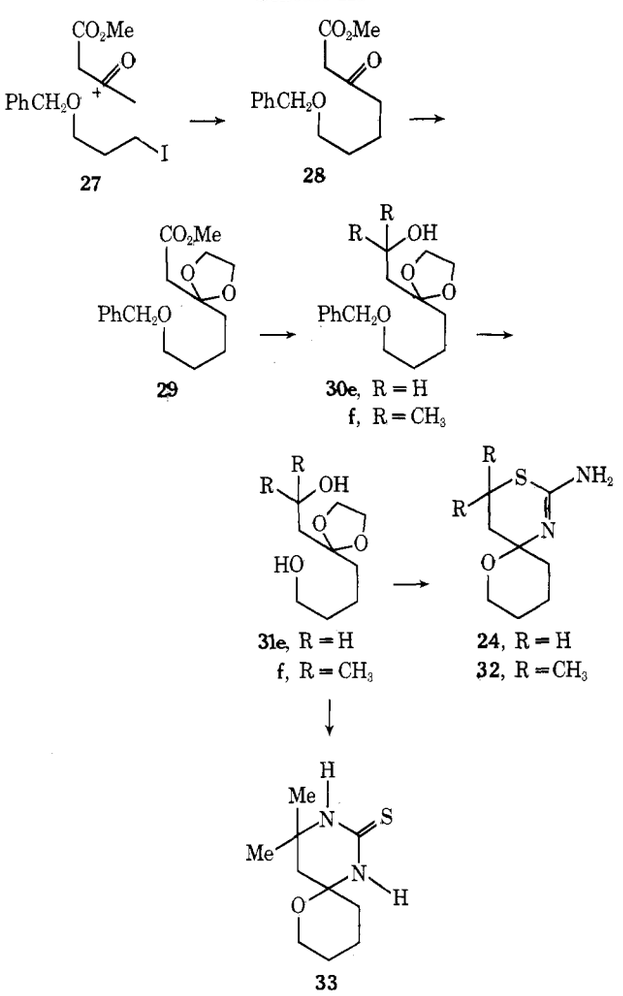
required. In contrast to the behavior of the 5-substituted $\delta$-lactones **14**, $\delta$-valerolactone itself was not converted into **19** upon treatment with vinylmagnesium chloride at low temperature.[25] We therefore turned our attention to the preparation of intermediates such as **20**. Reaction of 5-hydroxypentanal (**21**)[26] (Scheme II) with vinylmagnesium chloride gave the diol **22**,[27] which yielded the required Mannich base **23** (**20**, X = $NEt_2$, R = O)[10] in 51% overall yield upon selective oxidation with manganese dioxide in the presence of diethylamine.[21] Condensation of **23** with thiourea in refluxing toluene–acetic acid produced the desired spirothiazinepyran **24** in 45–55% yield. It was subsequently found that condensation of the Mannich bases **26a** and **26c** (prepared from **4a** and **4c** by addition of diethylamine) with thiourea under these conditions afforded the same mixtures of epimeric amino thiazines **15a, 16a** and **15c, 16c** as were obtained directly from **4a** and **4c**.

It is interesting to note that, when **23** was first quaternized with methyl iodide and the resulting salt was heated with thiourea in pyridine, a compound isomeric with

**Scheme II**




**Scheme III**



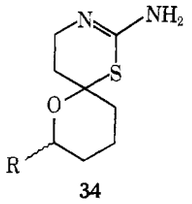

**24** was isolated in 24% yield. We have assigned the pyrimidinethione structure **25** to this material on the basis of its spectral properties, most notably the absorption in the ultraviolet at 244 nm characteristic of thioureas.[28] The formation of related pyrimidinethiones from the reaction of thiourea with $\alpha,\beta$-unsaturated ketones has been reported previously.[12,14,16]

An alternative synthesis of **24** is shown in Scheme III. Alkylation of the dianion of methyl acetoacetate[29] with 3-benzyloxypropyl iodide (**27**)[30] gave the $\beta$-keto ester **28** in 60% yield. Formation of the corresponding ethylene ketal **29** was followed by lithium aluminum hydride reduction, yielding the hydroxy ketal **30e**. Removal of the benzyl protecting group by catalytic hydrogenolysis then furnished the diol **31e** (**20**, X = OH; R = $-OCH_2CH_2O-$), which, in turn, produced **24** (isolated as the maleic acid salt in 55% overall yield based on **28**) upon reaction with thiourea in refluxing aqueous sulfuric acid.

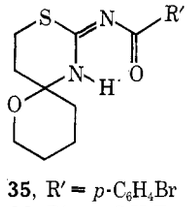
An attempt was made to extend this scheme to the synthesis of compound **32**, the 4,4-dimethyl analog of **24**. Thus, treatment of ketal ester **29** with methyllithium gave the carbinol **30f**, which was subjected to catalytic hydrogenolysis affording diol **31f**. Unfortunately, reaction of **31f** with thiourea in aqueous acid gave a complex mixture from which none of the expected thiazine **32** could be isolated. Instead, the only characterizable compound produced in this reaction was the isomeric pyrimidinethione **33**, which was obtained in very low yield.

It was of interest to confirm the structures of these novel spirothiazinepyrans. In particular, we wished to exclude definitively the isomeric thiazines represented by

34, which, although less likely to be formed on the basis of precedent,[2,12-16] were nonetheless conceivable products from the reaction of thiourea with our vinyl ketones or vinyl ketone precursors. To this end, an X-ray analysis of compound **35**, the *p*-bromobenzoyl derivative of **24**, was carried out. A view of the molecule is shown in Figure 1. Besides confirming the expected placement of the heteroatoms, two other important structural features of the crystal structure determination should be noted. First of all, it is evident that the amidine proton resides on the endocyclic nitrogen atom and is strongly hydrogen bonded to the carbonyl oxygen atom. The uv maxima and virtual lack of normal carbonyl absorption in the ir spectra exhibited by these compounds are consistent with this structural arrangement.[31] Secondly, in the solid state, this molecule assumes the expected[24] conformation in which the thiazine ring nitrogen is axial with respect to the pyran ring and the pyran ring oxygen is axial with respect to the thiazine ring.[34]



**34**



**35**, R′ = *p*-$C_6H_4Br$
**36**, R′ = *p*-$C_6H_4F$

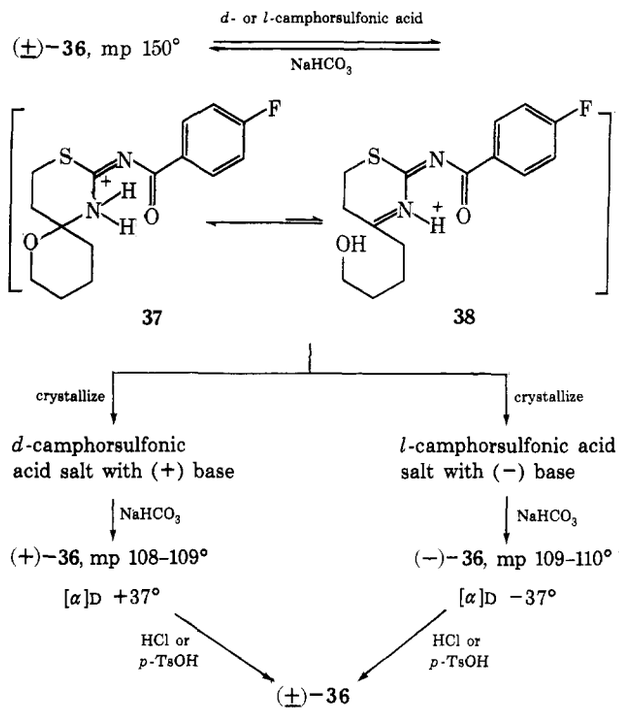
During the course of this work, we studied the optical resolution of the *p*-fluorobenzoylimino derivative **36**[35] (Scheme IV). Thus, treatment of this substance with *d*-(+)-10-camphorsulfonic acid in ethanol gave rise to a salt which was usually isolated in yields considerably greater than theoretical for one enantiomer. Basification of this salt gave an enantiomer of **36** showing $[\alpha]D$ + 37°. Similar results were obtained when *l*-(−)-10-camphorsulfonic acid[36] was employed, in which case the negatively rotating antipode was isolated. It was found that the enantiomers racemized readily on mild treatment with achiral acids such as hydrochloric or *p*-toluenesulfonic acid, regenerating **(±)-36**. When a solution of the resolved thiazine camphorsulfonic acid salt was neutralized with bicarbonate before crystallization could occur, the base obtained was racemic.

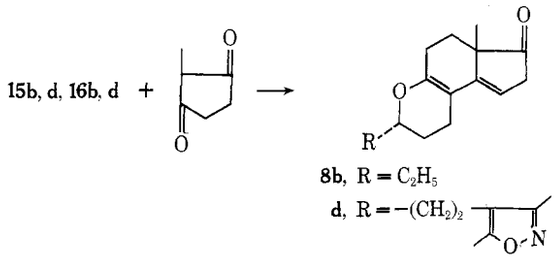
It soon became apparent that these molecules undergo facile ring-open-chain isomerism in the presence of acids, giving rise to a small concentration of an achiral species such as **38**[37] (or a tautomer) which is in rapid equilibrium with the spirocyclic cation **37** (or a tautomer). Fortuitously, in the presence of optically active camphorsulfonic acid, a salt precipitates which contains only one enantiomer of the spiro compound. As a practical consequence of this phenomenon, the enantiomers of **36** could be produced from the racemic modification in weight yields exceeding 80%.

A further manifestation of this ring-open-chain isomerism was observed when the pure 8-methyl epimer **17a** (R′ = $CH_3$) was hydrolyzed in aqueous hydrochloric acid. This reaction produced the mixture of epimeric amines **15a** and **16a**, indicating that equilibration of the 8-methyl group had taken place again *via* facile ring opening and reclosing. Reacetylation of this mixture gave a mixture of **17a** and **18a** with the former predominating as evidenced by nmr and tlc analysis.

We stated at the outset that the original aim of this work was a search for novel intermediates of potential utility in steroid total synthesis. Although the spirothiazinepyrans obtained were not the intermediates envisioned, they nonetheless seemed to be potentially capable of conversion into the dienes **8**. In the event, it was found that the reaction of the thiazine mixture **15d** and **16d** with 2-methyl-1,3-cyclopentanedione in the presence of aqueous acid was slow owing to the stability of the spiro compounds under these conditions. When these components were heated in refluxing aqueous dioxane containing *p*-toluenesulfonic acid for 92 hr, and the crude, neutral product was dehydrated with *p*-toluenesulfonic acid in benzene, the desired diene **(±)-8d**[20] was produced in 40% yield. In addition, 33% of the starting base mixture was recovered. Diene **(±)-8d** has previously been converted into racemic estr-4-ene-3,17-dione.[20] In a similar manner, diene **(±)-8b**[38] was produced in 33% yield from the mixture of spiro compounds **15b** and **16b**. The relatively low yields observed and stringent conditions required for the conversion of **15** and **16** to **8** indicate that these amino spirothiazinepyrans are inferior in utility to the Mannich bases **6** as intermediates in our steroid total synthesis. For this reason, optical resolution of the 8-substituted spiro bases and their conversion into the optically active dienes **8** was not investigated.

**Scheme IV**




## Experimental Section[39,40]

**δ-Lactones 14a-d.** (±)-5-Hydroxyhexanoic acid lactone (**14a**) was prepared by sodium borohydride reduction of 4-acetylbutyric acid followed by acidification in 86% yield, as a colorless liquid, bp 100–103° (10 mm) [lit.[17] bp 87–89° (7 mm)]. (±)-5-Hydroxyheptanoic acid lactone (**14b**) was synthesized in 76% yield by alkaline cleavage of 2-methyl-1,3-cyclohexanedione followed by sodium borohydride reduction of the crude keto acid and acidification, as a colorless liquid, bp 106–110° (6–7 mm) [lit.[18] bp 68–69° (1 mm)]. (±)-δ-Phenyl-δ-valerolactone (**14c**) was prepared as de-

scribed[19] by sodium borohydride reduction of 4-benzoylbutyric acid. The lactone, mp 72–74° (lit.[19] mp 74–76°), was obtained in 62% yield. (±)-7-(3,5-Dimethyl-4-isoxazolyl)-5-hydroxyheptanoic acid lactone (**14d**)[20] was provided by Dr. John W. Scott, Hoffmann-La Roche Inc., Nutley, N. J.

**Vinyl Ketones 4a–d.** These materials were prepared by treatment of the corresponding δ-lactones **14a–d** with vinylmagnesium chloride, in THF, at −50 to −60°, using the general procedure described previously.[9,20,21] The crude, oily vinyl ketones were used immediately, without purification.

**(±)-2-(2-Diethylaminoethyl)-6-methyltetrahydropyran-2-ol (26a).**[41] The crude vinyl ketone from 2.03 g (0.018 mol) of lactone **14a**, in ether solution, was treated with 10 ml of diethylamine. After standing at room temperature for 0.5 hr, the solution was concentrated at reduced pressure and the residue was partitioned between cold 1 *N* aqueous HCl and ether. The aqueous acidic solution was made alkaline with 20% aqueous KOH, saturated with salt, and worked up with ether, giving 2.6 g (68%) of Mannich base as a colorless oil: ir ($CHCl_3$) 3625–3125 (broad H-bonded OH), 1705 $cm^{-1}$ (weak ketone C=O of open form); nmr ($CDCl_3$) δ 4.08 (m, 1, $C_6$ H), 1.15 (d, $J$ = 7 Hz, $C_6$ $CH_3$), 1.10 ppm (t, $CH_3CH_2N$); mass spectrum $m/e$ 197 ($M - H_2O$).

**(±)-2-(2-Diethylaminoethyl)-6-phenyltetrahydropyran-2-ol (26c).** This material was prepared as in the preceding experiment. From 1.75 g (0.01 mol) of lactone **14c** there was obtained 1.55 g (55%) of Mannich base as a yellow oil: ir (film) 3600–3050 (broad H-bonded OH), 1705 $cm^{-1}$ (weak ketone C=O of open form).

**Preparation of the Racemic 8-Substituted 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes 15 and 16. A. From the Vinyl Ketones 4.** Solutions (1.0–1.6 *M*) of the crude, freshly prepared vinyl ketones **4a–d** in glacial acetic acid containing 1 molar equiv of thiourea (based on starting lactone **14**) were stirred at room temperature for 16–20 hr and then concentrated at reduced pressure. The residues were treated with ether and dilute (1–3 *N*) aqueous HCl. In series **a** and **d** the aqueous acidic layer was separated, washed once with ether (the ether layers were discarded), and then made alkaline with 10% aqueous NaOH. Extraction with dichloromethane yielded the mixtures of products **15** and **16.** In series **b,** a crystalline hydrochloride salt was obtained from the acidic aqueous solution, which was filtered and washed with ice-water. After drying, an almost colorless solid, mp 213–214.5° dec, was isolated in 22.4% yield. Tlc analysis (system A) indicated that the free base derived from this salt was largely the major, less polar epimer **15b.** The filtrate and washes were combined and made alkaline with concentrated $NH_4OH$. Extraction with dichloromethane gave the mixture of amines **15b** and **16b** as a viscous, brown oil, in 41% yield. The minor epimer **16b** was never isolated in pure form. A sample of the above salt was recrystallized from water to give an analytical specimen as a slightly off-white solid, mp 211–212°.

*Anal.* Calcd for $C_{10}H_{18}N_2OS \cdot HCl$: C, 47.89; H, 7.64; N, 11.17; S, 12.78. Found: C, 48.12; H, 7.75; N, 11.44; S, 12.31.

In the **c** series, addition of ether and 1 *N* aqueous HCl to the crude product after removal of the acetic acid led to the formation of a dense precipitate of HCl salt. The solid was filtered and the aqueous portion of the filtrate was separated from the ether layer and combined with the solid HCl salt before being made alkaline with 10% aqueous NaOH. Isolation with dichloromethane gave the mixture of epimers **15c** and **16c** as an orange semisolid.

In all four series, tlc analysis (system A) of the crude, basic product showed two spots, $R_f$ ~0.4 (major, **15**) and ~0.13 (minor, **16**). Separation of the isomers was carried out using the following procedures.

**Series a.** The crude reaction product was triturated with benzene and the resulting solid, which was largely **16a** (tlc), was filtered off. The benzene mother liquor was concentrated and the residue was purified by dry-column chromatography on 500 parts by weight of Woelm grade III neutral alumina. After development with 9:1 ethyl acetate–triethylamine, elution with methanol gave pure **15a** as a viscous oil. This material could not be induced to crystallize but was treated with 0.58 g of maleic acid and the resulting salt was recrystallized from ethyl acetate and then acetonitrile, giving a colorless solid, mp 139–141°.

*Anal.* Calcd for $C_9H_{16}N_2OS \cdot C_4H_4O_4$: C, 49.36; H, 6.37; N, 8.86; S, 10.12. Found: C, 49.47; H, 6.50; N, 8.75; S, 10.14.

**Series c.** The crude base mixture was triturated with ethyl acetate and filtered, giving essentially pure **16c** as a colorless solid. The mother liquor was diluted with ethyl acetate, stirred with approximately 25 parts by weight of Woelm grade I neutral alumina, and then filtered. Concentration of the filtrate gave pure **15c** as an oil which crystallized on standing.

**Series d.** Repeated recrystallization of a sample of the crude semisolid base mixture from acetonitrile gave pure **15d.** Dry-column chromatography of a sample of this base mixture on 400 parts by weight of Woelm grade III neutral alumina, developing with 9:1 benzene–triethylamine, furnished a nearly pure sample of **16d** (eluted with methanol).

**B. From the Mannich Bases 26.** A mixture of 10 g (0.0465 mol) of Mannich base **26a,** 3.65 g (0.048 mol) of thiourea, 35 ml of glacial acetic acid, and 105 ml of toluene was stirred and heated at reflux for 75 min. The resulting solution was cooled, extracted with 3 *N* aqueous HCl, and discarded. The aqueous acidic extract was made alkaline with 10% aqueous NaOH and worked up with ether, giving 6.9 g of semisolid product, tlc analysis of which indicated that it was identical with the crude mixture of **15a** and **16a** derived from vinyl ketone **4a.**

Using essentially the same procedure, the Mannich base **26c** (1.55 g, 0.0056 mol) was treated with thiourea (0.44 g, 0.0058 mol). The reaction mixture was cooled, diluted with ether, and treated with 3 *N* aqueous HCl. The resulting precipitated hydrochloride salt was filtered and then treated with 10% aqueous NaOH. Extraction with dichloromethane gave 1.1 g of the mixture **15c** and **16c.** Tlc analysis showed the same two spots in approximately the same proportion as exhibited by the crude product derived from **4c.**

Physical properties and microanalytical, spectral, and yield data for the amino thiazines are presented in Table I.

**6-Heptene-1,5-diol (22).** A 2.91 *M* solution of vinylmagnesium chloride in THF (970 ml) was stirred efficiently while a solution of 96 g (0.94 mol) of 5-hydroxypentanal[26] in 250 ml of THF was added dropwise over a 30-min period. Ice-bath cooling was employed to maintain the internal temperature at 30°. The resultant gelatinous yellow-brown mixture was stirred at room temperature for 2 hr, then again cooled in an ice bath, and cautiously hydrolyzed with 500 ml of saturated aqueous $NH_4Cl$. It should be noted that, after the addition of approximately 20 ml of the $NH_4Cl$ solution, a white, viscous mass formed and the remainder of the solution had to be added with *extreme care* until the mixture thinned and the mechanical stirrer was again able to operate smoothly. When the hydrolysis was complete, the suspension was filtered and the salts were washed several times with ether. The filtrate and washes were combined, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo.* Distillation of the residue gave 90 g (74%) of diol **22** as a colorless liquid, bp 100–105° (0.3 mm) [lit.[27] bp 105–107° (0.6 mm)].

**2-(2-Diethylaminoethyl)tetrahydropyran-2-ol (23).** A solution of 90 g (0.69 mol) of diol **22** in 2500 ml of 1,2-dichloroethane (shaken with anhydrous $K_2CO_3$ and filtered before use) and 400 ml of diethylamine was stirred efficiently with ice-bath cooling while 750 g of activated manganese dioxide[21,42] was added in portions over a 15-min period. The resulting slurry was stirred for 24 hr at room temperature and then the solids were filtered and washed thoroughly with benzene. The filtrate and washes were combined and concentrated at reduced pressure, giving 110 g of dark brown oil. This material was dissolved in 150 ml of ethyl acetate and the resulting solution was cooled in an ice bath while 700 ml of 1.2 *N* aqueous HCl was slowly added with stirring. The mixture was then extracted with three 300-ml portions of ethyl acetate and the ethyl acetate extracts were combined, washed with saturated brine (300 ml), and then discarded. The aqueous solutions were combined and made alkaline by the cautious addition, with cooling, of approximately 150 ml of 10 *N* aqueous NaOH, and then the product was isolated by benzene extraction. This afforded 96.4 g (69%) of Mannich base **23** as a brown oil. A sample was chromatographed on 50 parts of Woelm grade III neutral alumina. Elution with benzene gave pure (tlc, system A) **23,** ir (film) 3100–3600 (H-bonded OH), 1715 $cm^{-1}$ (w, C=O of open form).

*Anal.* Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.80; H, 11.52; N, 6.69.

**3-Benzyloxy-1-propyl Iodide (27).** 3-Benzyloxy-1-propanol was prepared from trimethylene glycol and converted into 3-benzyloxy-1-propyl chloride with thionyl chloride and *N,N*-dimethylaniline using the procedures described by Bennett and Hock.[43] The iodide was obtained in 94% yield by treatment of the chloride with excess sodium iodide in refluxing 2-butanone, as a yellow liquid, bp 96–110° (0.2–0.5 mm) [lit.[30] bp 112–113° (1.1 mm)].

**Methyl 3-Oxo-7-benzyloxyheptanoate (28).** The procedure of Weiler[29] was employed. A slurry of sodium hydride from 8.1 g

(0.169 mol) of 50% sodium hydride–mineral oil dispersion washed free of mineral oil with hexane, in 300 ml of dry THF was stirred with ice-bath cooling while a solution of 17.4 g (0.15 mol) of methyl acetoacetate in 30 ml of THF was added dropwise during 20 min ($H_2$ evolution). Stirring was continued for 20 min at 0–5°, whereupon 68 ml (0.162 mol) of 2.38 *M* butyllithium in hexane was added dropwise over 25 min, keeping the temperature around 10°. The orange mixture was stirred for 10 min with ice-bath cooling and then a solution of 45 g (0.163 mol) of 3-benzyloxypropyl iodide (**27**) in 45 ml of THF was added during 25 min, keeping the temperature below 20°. The ice bath was removed and stirring was continued for 45 min; then the reaction mixture was cautiously poured into a mixture of ice and 3 *N* aqueous HCl. The organic materials were isolated with ether (the combined ether extracts were additionally washed with aqueous sodium bisulfite), giving 45.8 g of an orange liquid. This material was chromatographed on 400 g of silica gel. Elution with 9:1 hexane–ether gave 13.5 g (30%) of recovered iodide. Elution with 4:1–1:3 hexane–ether furnished 23.7 g (59.7%) of pure keto ester **28** as a yellow liquid.

In another run a sample of keto ester prepared in this way was evaporatively distilled, giving a pale-yellow liquid: bp 150–190° (bath, 0.05 mm); ir ($CHCl_3$) 1745 (ester C=O), 1720 $cm^{-1}$ (ketone C=O); nmr ($CDCl_3$) $\delta$ 7.27 (s, 5, $C_6H_5$–), 4.45 (s, 2, $C_6H_5CH_2O$–), 3.67 (s, 3, $-CO_2CH_3$), 3.45 (m, 2, $C_7H$), 3.38 (s, 2, $C_2$ H), 2.53 (m, 2, $C_4$ H), 1.65 ppm (m, 4, $C_5$ H, $C_6$ H); mass spectrum *m/e* 264 ($M^+$), 91 (base).

*Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.33; H, 7.80.

**Methyl 7-Benzyloxy-3,3-ethylenedioxyheptanoate (29).** A mixture of 2.65 g (0.01 mol) of keto ester **28**, 1 g (0.0162 mol) of ethylene glycol, 0.06 g of *p*-toluenesulfonic acid monohydrate, and 30 ml of benzene was stirred and heated at reflux for 2.5 hr. A Dean-Stark trap was employed to collect water (0.35 ml). After cooling, the mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate solution and brine, and then the organic solution was dried, filtered, and concentrated at reduced pressure, giving 3.05 g (98.7%) of ketal **29** as a yellow oil: ir ($CHCl_3$) 1740 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) $\delta$ 7.28 (s, 5, $C_6H_5$–), 4.45 (s, 2, $C_6H_5CH_2O$–), 3.91 (s, 4, $-OCH_2CH_2O$–), 3.63 (s, 3, $-CO_2CH_3$), 3.45 (t, 2, $J$ = 6 Hz, $C_7$ H), 2.26 (s, 2, $C_2$ H), 1.66 ppm (m, 6, $C_{4-6}$ H); mass spectrum *m/e* 308 ($M^-$), 235, 145 (base), 91.

**3,3-Ethylenedioxy-7-benzyloxyheptan-1-ol (30e).** A solution of 2.6 g (8.45 mmol) of ketal ester **29** in 50 ml of dry ether was added dropwise over a 20-min period to a stirred mixture of 0.65 g (17.1 mmol) of lithium aluminum hydride in 50 ml of dry ether, with ice-bath cooling. Stirring was continued at 0–5° for 20 min and then at room temperature for 80 min. The reaction mixture was again cooled in an ice bath and cautiously decomposed by the addition of 1.3 ml of water and 1 ml of 10% aqueous NaOH. After stirring at room temperature for 45 min, the mixture was filtered and the solids were washed well with ether. The filtrate and washes were combined and concentrated at reduced pressure, giving 2.25 g (95.2%) of **30e** as a pale-pink oil. The crude alcohol could be used in the ensuing reactions without purification.

This material was chromatographed on 100 g of silica gel. Elution with 1:1 benzene–ether gave 1.95 g (82.5%) of pure **30e** as a pale-yellow oil: ir ($CHCl_3$) 3550 $cm^{-1}$ (OH); nmr ($CDCl_3$) $\delta$ 7.31 (s, 5, $C_6H_5$–), 4.48 (s, 2, $C_6H_5CH_2O$–), 3.93 (s, 4, $-OCH_2CH_2O$–), 3.73 (m, 2, $C_1$ H), 3.47 (m, 2, $C_7$ H), 2.75 (m, 1, -OH), 1.90 (t, $J$ = 6 Hz, 2, $C_2$ H), 1.58 ppm (m, 6, $C_{4-6}$ H); mass spectrum *m/e* 280 ($M^+$), 117 (base).

*Anal.* Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.60; H, 8.46.

**3,3-Ethylenedioxy-1,7-heptanediol (31e).** A 1.6-g (5.72 mmol) sample of alcohol **30e** was hydrogenated in 30 ml of ethanol over 0.2 g of preequilibrated 5% palladium on carbon catalyst at ~1 atm. After 1.5 hr, hydrogen uptake ceased. A total of 141 ml of hydrogen was consumed (143 ml theory). The catalyst was filtered on a Celite pad and washed with ethanol. Concentration of the combined filtrate and washes gave 1.02 g (94.3%) of diol **31e** as an almost colorless oil, ir ($CHCl_3$) 3625, 3500 $cm^{-1}$ (OH); the ir, nmr, and mass spectra indicated the absence of the benzyl group.

**(±)-2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (24). A. From Mannich Base 23.** A solution of 60 g (0.298 mol) of the Mannich base **23** and 22.8 g (0.3 mol) of thiourea in 940 ml of toluene and 300 ml of glacial acetic acid was stirred and heated at reflux for 3 hr, using a Dean-Stark trap to remove water. At the end of this time, 15 ml of water–acetic acid layer had been collected and essentially no more water was being formed. The resulting dark red solution was cooled and the solvents were removed at 50–60°, under aspirator pressure and finally high vacuum. The oily residue was stirred rapidly and cooled in an ice bath while 500 ml of 10% aqueous NaOH was slowly added. After the addition was complete (pH 11–12), the mixture was stirred rapidly for 10 min with ice-bath cooling and then filtered with suction. The solid was washed with water and then dried under high vacuum, giving 35.9 g of crude **24** as a tan solid. Recrystallization from about 200 ml of ethyl acetate gave 25.9 g (46.8%) of large, tan crystals, mp 137.5–139°. Tlc analysis (system A) showed essentially a single spot, $R_f$ 0.25. Several repetitions of this procedure gave yields in the range of 45–55%. An analytical specimen of **24** was obtained by further recrystallization of a sample from ethyl acetate, as a colorless solid: mp 139–140.5°; ir (KBr) 3375, 3300, 3250, 3150 (NH), 1640, 1590 $cm^{-1}$ (C=N); nmr (DMSO-$d_6$) $\delta$ 3.90 ppm (m, $C_8$ H); mass spectrum *m/e* 186 ($M^+$), 158 ($M - C_2H_4$).

*Anal.* Calcd for $C_8H_{14}N_2OS$: C, 51.60; H, 7.58; N, 15.04; S, 17.19. Found: C, 51.68; H, 7.70; N, 15.25; S, 17.44.

The maleic acid salt was obtained as a colorless solid, mp 164–165°, by recrystallization from ethanol.

*Anal.* Calcd for $C_8H_{14}N_2OS \cdot C_4H_4O_4$: C, 47.68; H, 6.00; N, 9.27; S, 10.59. Found: C, 47.41; H, 5.78; N, 9.19; S, 10.71.

**B. From Diol Ketal 31e.** A solution of 0.954 g (5 mmol) of diol **31e** and 0.4 g (5.26 mmol) of thiourea in 25 ml of 0.5 *N* aqueous $H_2SO_4$ was stirred and heated at reflux for 2 hr. After cooling, the reaction mixture was made alkaline with 10% aqueous NaOH and saturated with salt and the product was isolated by extraction with dichloromethane, giving 0.762 g (82%) of crude **24** as a pale-yellow solid. This material was dissolved in hot ethanol and treated with 0.475 g of maleic acid. There was obtained 0.93 g (61.6%) of colorless, crystalline salt, mp 160–163°.

**(±)-7-Oxa-1,3-diazaspiro[5.5]undecane-2-thione (25).** A solution of 5 g (0.0249 mol) of Mannich base **23** in 20 ml of acetone was treated with 5 ml of methyl iodide and allowed to stand overnight at room temperature. The solvents were removed under reduced pressure, giving 8.9 g of gummy methiodide. To this was added 1.9 g (0.025 mol) of thiourea and 35 ml of pyridine. The reaction mixture was stirred and heated at 100° for 4 hr, then the pyridine was removed at reduced pressure. The residue was treated with 30 ml of water, basified to pH 11 with 10% aqueous NaOH, and worked up with chloroform, giving a brown gum which crystallized on trituration with ethyl acetate. Digestion with boiling acetonitrile gave 1.1 g (23.8%) of off-white solid, mp 202–203°. Tlc analysis (system A) showed a single uv spot, $R_f$ 0.33. An analytical specimen was prepared by recrystallization of a sample from methanol–ether, giving a colorless solid: mp 204–205°; ir (KBr) 3200, 3100 (NH), 1560, 1500 $cm^{-1}$ (thiourea C=S); uv max (95% EtOH) 244 nm ($\epsilon$ 14,900); nmr (DMSO-$d_6$) $\delta$ 8.25 (m, 2, NH); mass spectrum *m/e* 186 ($M^+$).

*Anal.* Calcd for $C_8H_{14}N_2OS$: C, 51.60; H, 7.58; N, 15.04; S, 17.19. Found: C, 51.50; H, 7.62; N, 15.05; S, 17.37.

**Attempted Preparation of (±)-2-Amino-4,4-dimethyl-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (32).** A solution of 1 g (3.25 mmol) of ketal ester **29** in 20 ml of dry ether was added dropwise, over 10 min to 8 ml (13.2 mmol) of stirred 1.65 *M* ethereal methyllithium, with ice-bath cooling. Stirring was continued for 10 min at 0–5° and then at room temperature for 1.75 hr. At the end of this time, the reaction mixture was poured into ice water and worked up with ether, giving 0.95 g (95%) of yellow, oily 8-benzyloxy-4,4-ethylenedioxy-2-methyloctan-2-ol (**30f**): ir (film) 3500 $cm^{-1}$ (OH); nmr ($CDCl_3$) $\delta$ 7.32 (s, 5, $C_6H_5$–), 4.50 (s, 2, $C_6H_5CH_2O$–), 4.13 (s, $-OCH_2CH_2O$–), 3.48 (m, $C_8$ H), 1.92 (s, -OH), 1.24 ppm [s, $(CH_3)_2C$–].

A 0.883-g (2.87 mmol) sample of this crude alcohol was hydrogenated in 30 ml of ethanol, over 0.3 g of preequilibrated 5% palladium on carbon, at approximately 1 atm. A total of 87 ml of hydrogen was absorbed during 15 min (72 ml theory). The catalyst was filtered and washed with ethanol and the combined filtrate and washes were concentrated at reduced pressure, giving 0.571 g of colorless, oily diol **31f**, ir (film) 3375 $cm^{-1}$ (OH).

A solution of 1.24 g (5.69 mmol) of diol **31f** prepared in this way, 0.435 g (5.72 mmol) of thiourea, 0.18 ml of water, and 25 ml of glacial acetic acid was stirred at room temperature for 0.5 hr then at reflux for 3.25 hr, and again at room temperature for 14 hr. The resulting solution was concentrated at reduced pressure, giving 2.1 g of yellow oil the ir spectrum of which showed strong bands at 1740 and 1245 $cm^{-1}$, indicating the presence of acetate esters.

This material was treated with 5 ml of 10% aqueous NaOH so-

lution and 15 ml of methanol and the resulting solution was stirred at room temperature for 1.25 hr and then poured into brine, whereupon the organic materials were isolated by extraction with dichloromethane. This afforded 1.0 g of a yellow, semisolid product which was treated with ether and 1 *N* aqueous $H_2SO_4$. The resulting solid was filtered, washed with ether and water, and dried, giving 0.19 g of crude (±)-4,4-dimethyl-7-oxa-1,3-diazaspiro[5.5]undecane-2-thione (**33**) as a colorless solid.

A 0.211-g sample of **33** prepared in this way was chromatographed on 10 g of silica gel. Elution with chloroform gave 0.16 g of pure **33** as a colorless solid which was recrystallized from ethanol, yielding colorless crystals (0.122 g): mp 196.5–198°; ir (KBr) 3225 (NH), 1560, 1510 $cm^{-1}$ (thiourea C=S); uv max (95% EtOH) 247 nm ($\epsilon$ 15,800); nmr (DMSO-$d_6$) $\delta$ 8.28 (m, 1, -NH), 8.11 (m, 1, -NH), 3.55 (m, 2, $C_8$ H), 1.26 (s, $C_4$ $CH_3$), 1.17 ppm (s, $C_4$ $CH_3$); mass spectrum *m/e* 214 ($M^+$, base), 139.

*Anal.* Calcd for $C_{10}H_{18}N_2OS$: C, 56.04; H, 8.47; N, 13.07; S, 14.96. Found: C, 56.09; H, 8.49; N, 13.18; S, 14.96.

The above aqueous sulfuric acid solution was made alkaline with aqueous NaOH and the organic materials were isolated with dichloromethane. This gave 0.385 g of a yellow gum, tlc analysis of which indicated a complex mixture.

**Acylation of the 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes.** The following general procedure was employed for preparation of **17a–c** and **18a–c** (R′ = $CH_3$). A solution of 0.05 mol of the mixture of amines **15** and **16** in 10 ml of pyridine and 5 ml of acetic anhydride was kept at room temperature for 3–20 hr and then concentrated at reduced pressure. The residue was dissolved in ether and the ether solution was washed three times with 1 *N* aqueous HCl. The aqueous acid extracts were combined and washed once with ether (the ether solutions containing neutral impurities were discarded), then made alkaline with 10% aqueous NaOH and saturated with NaCl. The products were then isolated by ether extraction and showed two spots on tlc analysis (system B), $R_f$ ~0.30 (**17**) and ~0.20 (**18**). These mixtures were separated by column chromatography on 50 parts by weight of silica gel. Elution with 4:1 benzene–ether gave the less polar epimer **17** (R′ = $CH_3$), whereas elution with 1:1 benzene–ether and ether furnished **18** (R′ = $CH_3$). In the 8-phenyl series, acetylation of the crude amine mixture **15c** and **16c** by this procedure gave the corresponding mixture of derivatives **17c** and **18c** (R′ = $CH_3$). The nmr spectrum exhibited acetyl methyl singlets at $\delta$ 2.13 (**17c**) and 2.08 ppm (**18c**) in a ratio, by integration, of approximately 3:1, respectively.

The benzoylimino derivatives **17c** and **18c** (R′ = *p*-$C_6H_4Br$), **35**, and **36** were prepared by stirring a 0.3–0.8 *M* pyridine solution of the amine **24** or amine mixture **15c** and **16c** at 0° while the aroyl chloride (1 equiv) was added. The resulting mixture was stirred at room temperature for 3–6 hr and then treated with saturated aqueous $NaHCO_3$. Work-up with ether or dichloromethane gave the products, which were purified by chromatography on silica gel and/or recrystallization. The mixture of epimers **17c** and **18c** (R′ = *p*-$C_6H_4Br$) was separated by chromatography on 50 parts by weight of silica gel. Elution with 1:1 hexane–ether gave the major and less polar epimer **17c** (R′ = *p*-$C_6H_4Br$) (tlc, $R_f$ 0.45, system C). Elution with 1:2 hexane–ether afforded the minor epimer **18c** (R′ = *p*-$C_6H_4Br$).

Physical properties and microanalytical and spectral data of the acyl derivatives are presented in Table II.

**(+)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(+)-36] *d*-(+)-Camphorsulfonic Acid Salt.** A mixture of 10.1 g (0.032 mol) of racemic 2-*p*-fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [**(±)-36**], 7.6 g (0.0328 mol) of *d*-(+)-camphorsulfonic acid, and 250 ml of ethanol was heated until all the solids had dissolved and then concentrated to a volume of approximately 70 ml at reduced pressure. After standing at room temperature for 2 hr and at 0° for 16 hr the solid was filtered, washed with ethanol and dried, giving 8.9 g (50.3%) of colorless solid, mp 149.5–151°. Two recrystallizations from ethanol gave colorless crystals, mp 149.5–151°, $[\alpha]^{25}D$ −22.61° (*c* 0.9862, $CHCl_3$).

*Anal.* Calcd for $C_{15}H_{17}FN_2O_2S \cdot C_{10}H_{16}O_4S$: C, 55.54; H, 6.15; N, 5.18; S, 11.86. Found: C, 55.66; H, 6.30; N, 5.19; S, 11.93.

In a subsequent experiment, carried out on the same scale, reduction of the amount of ethanol used in the initial crystallization to 50 ml allowed isolation of this salt in two crops of 12.6 g (mp 147.5–149.5°) and 1.8 g (mp 142–147°) for a total weight yield of 82%.

**(+)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(+)-36].** A 0.3-g sample of the salt prepared in the previous experiment was shaken with saturated aqueous $NaHCO_3$ and the liberated base was extracted with dichloromethane, giving 0.169 g of colorless solid **(+)-36,** mp 108.5–109.5°, $[\alpha]^{25}D$ +36.71° (*c* 0.9780, $CHCl_3$). The spectral and tlc properties of this material were essentially identical with those of the racemic form.

*Anal.* Calcd for $C_{15}H_{17}FN_2O_2S$: C, 58.43; H, 5.56; N, 9.08; S, 10.40. Found: C, 58.58; H, 5.69; N, 9.14; S, 10.27.

**(−)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(−)-36] *l*-(−)-Camphorsulfonic Acid Salt.** A mixture of 8.0 g (0.026 mol) of **(±)-36,** 6.2 g (0.027 mol) of *l*-(−)-camphorsulfonic acid,[36] and 100 ml of ethanol was heated until all the solids had dissolved and then concentrated at reduced pressure. The residue was recrystallized from approximately 45 ml of ethanol. This gave 9.5 g (67.7%) of colorless solid, mp 148.5–150°. Another recrystallization from ethanol (30 ml) gave 7.2 g of colorless solid salt, mp 148.5–150°, $[\alpha]^{25}D$ +19.57° (*c* 1.017, $CHCl_3$).

*Anal.* Calcd for $C_{15}H_{17}FN_2O_2S \cdot C_{10}H_{16}O_4S$: C, 55.54; H, 6.15; N, 5.18; S, 11.86. Found: C, 55.53; H, 6.23; N, 5.15; S, 11.71.

In a subsequent experiment, 10 g of **(±)-36** and 7.7 g of *l*-(−)-camphorsulfonic acid crystallized from 35 ml of ethanol gave 14.4 g (82%) of salt, mp 147.5–150°.

**(−)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(−)-36].** A 6.4-g sample of the salt prepared in the previous experiment was shaken with excess aqueous saturated $NaHCO_3$ and the mixture was extracted with dichloromethane, giving 3.45 g of **(−)-36** as a colorless solid, mp 109–110°, $[\alpha]^{25}D$ −36.76° (*c* 1.020, $CHCl_3$). The spectral and tlc properties of this material were essentially identical with those of the racemic form and the (+) enantiomer.

*Anal.* Calcd for $C_{15}H_{17}FN_2O_2S$: C, 58.43; H, 5.56; N, 9.08; S, 10.40. Found: C, 58.23; H, 5.64; N, 9.10; S, 10.14.

**Racemization of (+)-36. A.** A solution of 0.15 g of (+)-36 [$[\alpha]^{25}D$ +33.27° (*c* 1, $CHCl_3$)] and 0.01 g of *p*-toluenesulfonic acid monohydrate in 5 ml of ethanol was heated on a steam bath for 10 min and then poured into saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with dichloromethane, giving 0.142 g of colorless solid **(±)-36,** mp 147–149°, $[\alpha]^{25}D$ 0° (*c* 1, $CHCl_3$). No impurities were detected by tlc analysis (system B).

**B.** A suspension of 0.15 g of (+)-36 ($[\alpha]^{25}D$ +33.27°) in 15 ml of 0.1 *N* aqueous HCl was stirred at room temperature for 3 days and then treated with excess aqueous $NaHCO_3$. Extraction with dichloromethane gave 0.13 g of colorless solid **(±)-36,** mp 145.5–148°, $[\alpha]^{25}D$ +0.83° (*c* 1, $CHCl_3$). Tlc analysis showed that no impurities were present.

**C.** A 0.3-g sample of (+)-36 (+)-camphorsulfonic acid salt was dissolved in hot ethanol (15 ml) and the warm solution was poured into excess saturated aqueous $NaHCO_3$ solution. The liberated base was isolated by extraction with dichloromethane, giving 0.169 g of the pure (tlc) **(±)-36** as a colorless solid, mp 147–149°, $[\alpha]^{25}D$ 0° (*c* 1, $CHCl_3$).

**Acid Hydrolysis of 17a (R′ = $CH_3$).** A mixture of 1.57 g (6.52 mmol) of pure (tlc) **17a** (R′ = $CH_3$) and 20 ml of 2 *N* aqueous HCl was stirred and heated at reflux for 2 hr. After cooling, the reaction mixture was made alkaline with 10% aqueous NaOH and the products were isolated by extraction with dichloromethane. This gave 1.2 g of the amine mixture **15a** and **16a** as a yellow oil [tlc two spots, $R_f$ 0.07 (minor, **16a**) and 0.25 (major, **15a**), system A]. This material was acetylated as described above, giving an oily mixture of **17a** and **18a** (R′ = $CH_3$) in 89% yield. Analysis by tlc (system B) showed two spots with the less polar component (**17a**) predominating. The pmr spectrum ($CDCl_3$) showed two acetyl methyl singlets at $\delta$ 2.11 (**17a**) and 2.07 ppm (**18a**) in a ratio of approximately 3:2, respectively.

**(±)-*trans*-3-[2-(3,5-Dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7 (8*H*)-one [(±)-8d].** A solution of 0.927 g (3 mmol) of a mixture of amino thiazines **15d** and **16d** (mp 119–122°, predominantly **15d**), 0.375 g (3.34 mmol) of 2-methylcyclopentane-1,3-dione, and 0.12 g of *p*-toluenesulfonic acid monohydrate in 5 ml of water and 10 ml of dioxane was stirred and heated at reflux for 92 hr. The resulting solution was cooled, poured into dilute aqueous HCl, and then worked up by ether extraction (the ether extracts were additionally washed twice with saturated aqueous sodium bicarbonate solution; the aqueous acidic solution was saved for recovery of starting material), giving 0.57 g of an orange oil. This material was stirred and heated at reflux in 15 ml of benzene containing 29 mg of *p*-toluenesulfonic acid monohydrate for 40 min. A Dean-Stark trap was used to remove water. The resulting green solution was treated with aqueous $NaHCO_3$ and worked up with ether, yielding 0.47 g of crystalline product. Chromatography of this material on 25 g of silica gel afforded 0.398 g (40.6%) of essentially pure (tlc,

system B), crystalline diene (±)-8d, eluted with 19:1 benzene–ether. Recrystallization from 2-propanol gave 0.307 g of yellow crystals: mp 107–110°; uv max (95% EtOH) 253 nm (ε 20,100) [lit.[20] mp 113–116°; uv max (95% EtOH) 252 nm (ε 18,200)]. This material was essentially identical with an authentic sample of (±)-8d by tlc, ir, and nmr comparisons.

The aqueous acidic solution which had been set aside was made alkaline with 10% aqueous NaOH and extracted with ether, giving 0.31 g (33.4%) of recovered starting thiazine mixture.

**(±)-*trans*-3-Ethyl-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one [(±)-8b].** This material was obtained from reaction of the amino thiazine mixture **15b** and **16b** with 2-methyl-1,3-cyclopentanedione using the procedure described in the preceding experiment. From 1.25 g (5.84 mmol) of the thiazine mixture there was obtained 0.454 g (33.5%) of pure (tlc, system B) diene (±)-8b after chromatographic purification. Recrystallization from hexane–ether gave orange crystals: mp 101–103.5°; uv max (95% EtOH) 254 nm (ε 18,200) [lit.[38] mp 105–105.5°; uv max (95% EtOH) 254 nm (ε 17,600)]. The starting thiazine mixture recovered amounted to 41.2%.

**Crystallography.** Crystals of **35** are monoclinic, space group $P2_1/a$, with $a$ = 11.142 (6), $b$ = 14.117 (3), $c$ = 10.643 (4) Å, $\beta$ = 108.51 (4)°, $d_{obsd}$ (aqueous KI) = 1.53, $d_{calcd}$ = 1.544 g cm$^{-3}$ for $Z$ = 4.

The intensity data were measured on a Hilger-Watts Model Y290 diffractometer by a $\theta$–$2\theta$ technique. Ni-filtered Cu K$\alpha$ radiation and pulse height discrimination were used. Of the 3158 accessible reflections with $2\theta$ < 140°, 2097 had intensities significantly greater than background and these data were used for the structure analysis. The approximate size of the crystal used was 0.15 × 0.15 × 0.3 mm. The data were corrected for absorption ($\mu$ = 51.1 cm$^{-1}$).

The structure was solved by the heavy-atom method. The positions of the hydrogen atoms were obtained from a difference Fourier calculated after preliminary refinement of the heavier atoms. The final refinement was carried out by block diagonal least squares in which the crystal was partitioned into four blocks. Anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors for the hydrogen atoms. The positioned and thermal parameters of the hydrogen atoms were refined. The final discrepancy index, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, is 0.032 for the 2097 observed data.[44]

**Acknowledgments.** We wish to express our gratitude to the personnel of the Physical Chemistry Department of Hoffmann-La Roche Inc., Nutley, N. J., in particular Dr. W. Benz, Dr. T. Williams, Mr. S. Traiman, Dr. V. Toome, and Dr. F. Scheidl and their associates, for carrying out many of the spectral and microanalytical determinations required in this work. The technical assistance provided by Miss Roxanna Yang is also greatly appreciated.

**Registry No.**—**4a,** 51270-07-6; **4b,** 35313-18-9; **4c,** 51270-08-7; **4d,** 28867-67-6; **8b,** 35313-19-0; **8d,** 34769-94-3; **14c,** 51348-52-8; **15a,** 51270-09-8; **15a** maleate, 51270-10-1; **15b,** 51270-11-2; **15c,** 51270-12-3; **15d,** 51270-13-4; **16a,** 51270-14-5; **16c,** 51270-15-6; **16d,** 51270-16-7; **17a,** 51348-53-9; **17b,** 51348-54-0; **17c** (R′ = $CH_3$), 51348-55-1; **17c** (R′ = *p*-$C_6H_4Br$), 51348-56-2; **18a,** 51348-57-3; **18b,** 51348-58-4; **18c** (R′ = $CH_3$), 51348-59-5; **18c** (R′ = *p*-$C_6H_4Br$), 51348-60-8; **22,** 51270-17-8; **23,** 51270-18-9; **24,** 51270-19-0; **24** maleate, 51270-20-3; **25,** 51270-21-4; **26a,** 41323-55-1; **26c,** 41323-48-2; **27,** 5375-00-8; **28,** 51270-22-5; **29,** 51270-23-6; **30e,** 51270-24-7; **30f,** 51270-25-8; **31e,** 51270-26-9; **31f,** 51270-27-0; **33,** 51364-40-0; **35,** 51348-61-9; (±)-**36,** 51348-62-0; (+)-**36,** 51370-99-1; (+)-**36** *d*-(+)-camphorsulfonic acid salt, 51371-95-0; (−)-**36,** 51348-63-1; (−)-**36** *l*-(−)-camphorsulfonic acid salt, 51446-40-3; diethylamine, 109-89-7; thiourea, 62-56-6; 5-hydroxypentanal, 4221-03-8; methyl acetoacetate, 105-45-3; ethylene glycol, 107-21-1; *d*-(+)-camphorsulfonic acid, 3144-16-9; *l*-(−)-camphorsulfonic acid, 35963-20-3; 2-methylcyclopentane-1,3-dione, 765-69-5.

**Supplementary Material Available.** Listings of atomic parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1824.

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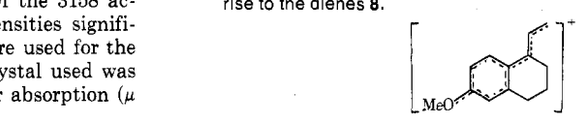
(10) These amine adducts exist preponderantly in the pseudo-spirocyclic, hydrogen-bonded hemiketal form, a factor which may be responsible for their relative ease of resolution.
(11) The related, stabilized carbenium ion i has been postulated as an intermediate species in the coupling of salt **2** with 2-methyl-1,3-cyclopentanedione.[2] Similarly, it is conceivable that the ion **10** may be involved in the reaction between the vinyl ketones **4** (or related derivatives such as **6**) and 2-methyl-1,3-cyclopentanedione, giving rise to the dienes **8**.

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(31) Monoacyl derivatives of 2-amino-5,6-dihydro-4*H*-1,3-thiazine have previously been described as the acylamino tautomer.[32,33] As can be seen in Table II, our acyl derivatives show a hypsochromic shift in the uv spectra when measured in 0.1 *N* HCl, indicating tautomerization to the acylamino form upon protonation.
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(35) This substance and many of its analogs, including **35,** show biological activity a description of which will be published elsewhere.
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terial was prepared by sulfonation of *l*-camphor using the procedure of P. D. Bartlett and L. H. Knox, *Org. Syn.*, **45**, 12 (1965); the acid obtained showed $[\alpha]^{25}D$ −20.54° (*c* 2, $H_2O$).

(37) Efforts to confirm the intermediacy of this or alternative open-chain species either by spectroscopic means or trapping experiments were unsuccessful. It is also conceivable, although seemingly less likely, that ring opening could occur *via* cleavage of the $C_6$–$N_1$ bond.

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(39) Unless otherwise noted, reaction products were isolated by addition of NaCl or saturated brine and extraction with the specified solvent. Organic extract solutions were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under water aspirator pressure at 40–50° on a rotary evaporator. The crude reaction products were then dried under high vacuum to constant weight. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an atmosphere of nitrogen. Unless otherwise noted, column chromatography was performed using Merck (Darmstadt) silica gel, 0.05–0.2 mm. Thin layer chromatography was performed using Brinkmann silica gel G plates with uv indicator. Plates were developed with one of the following systems: A, 9:1 benzene–triethylamine; B, 1:1 benzene–ethyl acetate; C, 1:1 hexane–ethyl acetate. Spots were detected with uv light, iodine vapor, or *p*-toluenesulfonic acid spray followed by heating. Varian A-60, HA-100, or Jeolco C-60H spectrometers were used to obtain the pmr spectra. Chemical shifts are reported relative to TMS as an internal standard. Infrared spectra were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. The ultraviolet spectra were recorded on a Cary Model 14M spectrophotometer. Low-resolution mass spectra were obtained on CEC 21-110 or JMS-01SG instruments. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Tetrahydrofuran (THF) and pyridine were dried by slurrying over Woelm grade I neutral alumina just prior to use.

(40) In naming the spiro compounds having an 8 substituent, we suggest that relative stereochemistry be designated by *c* and *t* to denote a cis or trans relationship to some reference (*r*) substituent. *Cf.* J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, **35**, 192 (1970); Beilstein, "Handbuch der Organischen Chemie," E III, Vol. VI, Part 7, p x. Thus, for example, compound **15a** would be named (±)-2-amino-8*t*-methyl-(6*r*N$^1$)-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene and the epimer **16a**, (±)-2-amino-8*c*-methyl-(6*r*N$^1$)-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene. With regard to the acyl derivatives, compound **17a** (R′ = $CH_3$), for example would be named (±)-2-acetylimino-8*t*-methyl-(6*r*N$^1$)-7-oxa-3-thia-1-azaspiro[5.5]undecane.

(41) This preparation was carried out by Mrs. Angela Duggan.

(42) *Cf.* N. Cohen, B. L. Banner, J. F. Blount, M. Tsai, and G. Saucy, *J. Org. Chem.*, **38**, 3229 (1973), for a description of the preparation of the manganese dioxide used in this oxidation.

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(44) See paragraph at end of paper regarding supplementary material.

# The Reaction of 3-Diazo-3*H*-indazole with Reactive Methylene Compounds and Formation of Indazolo[3,2-*c*]-1,2,4-triazines

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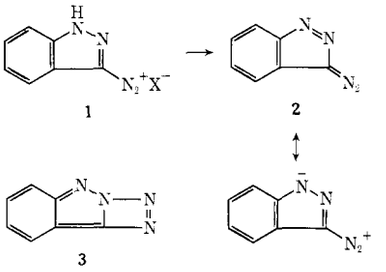
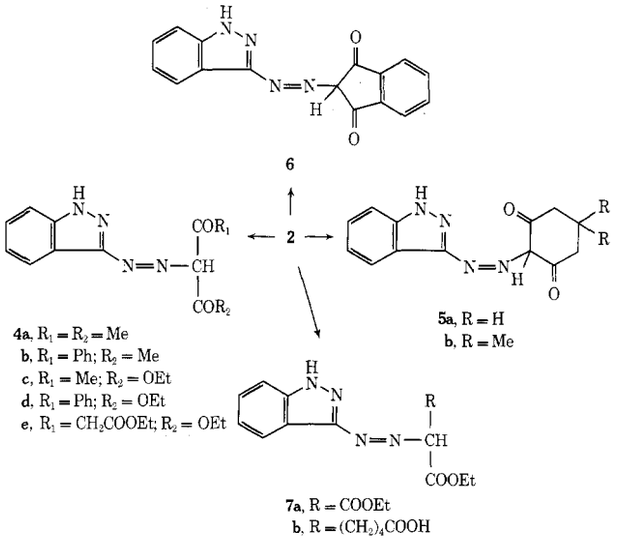
3-Diazo-3*H*-indazole reacts with 1,3-diketones, β-keto esters, or diethyl malonate and coupling occurs at the methylene group. The resulting products can be cyclized thermally or under the influence of acid into derivatives of indazolo[3,2-*c*]-1,2,4-triazine.

3-Aminoindazole, when diazotized, forms a diazonium salt (**1**) which can be converted upon treatment with alkali into the diazo compound. 3-Diazo-3*H*-indazole was the first heterocyclic diazo compound and was formulated by Bamberger[2] as indazolotriazolene (**3**), but later the diazo structure (**2**) was proposed.[3] 3-Diazo-3*H*-indazole exhibits



in solid state an ir absorption band at 2119 $cm^{-1}$, typical for diazo compounds,[4,5] and on the other hand it couples with phenols to give azo compounds or the diazo group can be replaced with halogens. So far, no other reactions of **2** have been investigated.

The reactivity of 3-diazo-3*H*-indazole was of interest in conjunction with our previous investigations on azido- and tetrazoloazines.[6-8] An ethanolic solution of **2**, when treated with a 1,3-dicarbonyl compound, a β-keto ester, or diethyl malonate, formed easily at room temperature the corresponding azo compound of the type **4**, **5**, **6**, or **7a**. Cyclic β-diketones, like cyclohexane-1,3-dione, its 5,5-dimethyl analog, or indan-1,3-dione, also reacted readily. For all compounds of this type several tautometric forms can be written. For example, compounds of the type **4** can be regarded as azo compounds or as hydrazones, and the carbonyl part can be written in the keto or enolized form. For compounds resulting from coupling of diazonium salts at a methyl or methylene carbon,[9] the hydrazone structure was postulated.[10] No attempt has been made to examine in detail the structures of our products.



Compound **5a**, from 3-diazo-3*H*-indazole and 2-carbethoxycyclohexanone, reacted in ethanolic solution at room temperature to afford **7b** after 48 hr, indicating that ring opening of the cyclohexanone ring occurred during