and 1665 cm^{-1}. It showed no optical activity, $[\alpha]^{18}D$ 0° (*c* 2.0, ethanol).

Registry No.—Silicon tetrachloride, 10026-04-7; trimethylacetoxysilane, 2754-27-0; dimethyldiacetoxysilane, 2182-66-3; tetraacetoxysilane, 562-90-3; 4-isobutyl-2-phenyloxazolone, 27460-46-4.

Some Observations on the Mechanism of a Modified Knorr Pyrrole Condensation[1a]

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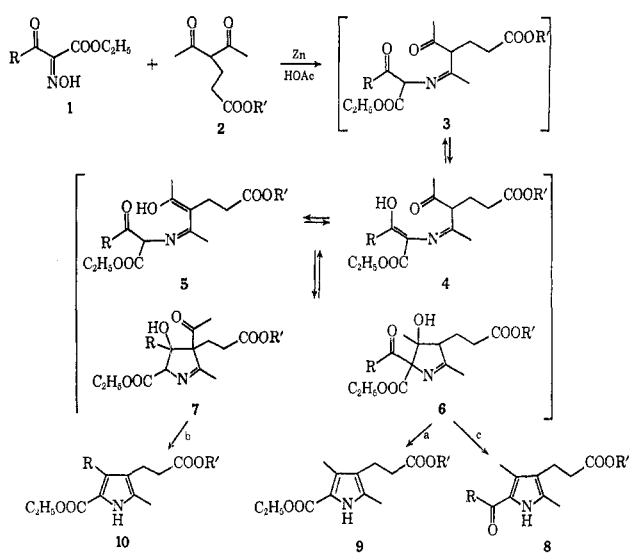
In preparing some pyrrolic intermediates for porphyrin synthesis *via* a modified Knorr condensation, contamination of the pyrrole by initially unidentified side products led us to a study of the effect of the structure of the β-keto ester on the mechanism of this reaction. It seemed conceivable that, in light of Scheme I, three

SCHEME I



pyrrolic products (**8**, **9**, and **10**) could be obtained. The postition of equilibrium between enols **4** and **5** and the relative rates of nucleophilic attack on the acyl groups of **6** and **7** are the factors which must be considered in deciding which pyrrole will predominate.

An earlier investigation of this condensation[2] showed that, when ethyl 4-acetyl-5-oxohexanoate (**2**, R′ = C_2H_5) was condensed with the oximino derivative of diethyl 3-oxoglutarate (**1**, R = CH_2COOEt), pyrrole **9** (R′ = C_2H_5) was isolated in 16.5% yield. Also, 3-methyl-2,4-pentanedione condensed with diethyl 2-oximino-3-oxoadipate (**1**, R = CH_2CH_2COOEt) to give 40% of the analogous structure, 2-carbethoxy-3,4,5-trimethylpyrrole. Since such a large percentage of starting materials remained unaccounted for, participation of path b was still a very real possibility, hence our investigation of the problem.

All of our condensations were carried out under standardized conditions (not optimized for maximum yields), and used the same β-diketone, namely, methyl 4-acetyl-5-oxohexanoate (**2**, R′ = CH_3); only the β-keto ester was varied. Ethyl acetoacetate-3-^{14}C, our first choice, afforded several advantages. First, there are no steric or electronic differences between the acyl groups that must be lost from **6** and **7**. Second, both **9** and **10** become structurally identical, eliminating any separation problem. Third, the fact that **10** is radioactively labeled permits a quantitative determination of the two potential pathways.

Labeled acetoacetic esters were converted to their oximino derivatives and condensed with an equimolar amount of **2** (R′ = CH_3). The pyrroles were isolated and purified, and their specific activities were compared to those of the starting β-keto esters. The results obtained in two experiments with the ethyl ester and one with the benzyl ester indicate that a is the major pathway for pyrrole formation (Table I).

TABLE I
CONDENSATION OF METHYL 4-ACETYL-5-OXOHEXANOATE (2) AND LABELED 2-OXIMINO-β-KETO ESTERS

β-Keto ester	Specific activity, dpm/mm, β-keto ester	Specific activity, dpm/mm, pyrrole	% path b	% yield of pyrrole (9 + 10)
Ethyl 2-oximinoacetoacetate-3-^{14}C, expt 1	39,960	470	1.2	45
Ethyl 2-oximinoacetoacetate-3-^{14}C, expt 2	27,890	440	1.6	37
Benzyl 2-oximinoacetoacetate-3-^{14}C	51,370	640	1.2	34

The mother liquors from the condensation with benzyl acetoacetate were then inspected for evidence of the presence of pyrrole **8** (R, R′ = CH_3) resulting from path c. Preparative tlc afforded a small amount of material identified as **8** by its uv absorption ($\lambda_{max}^{CH_3OH}$ 305 nm) and mass spectrum [*m/e* 223 (M^+, 56), 180 (5), 150 (100), 43 (48)], identical with an authentic sample prepared from 3,5-dimethyl-4-(β-carbomethoxyethyl)-2-carbethoxypyrrole by hydrolysis, decarboxylation, acetylation, and reesterification. However, its contribution was estimated to be much less than 1% of the total pyrrolic product.

The small contribution of path c in the reaction is understandable, since nucleophilic attack on **6** would prefer the more polar acetyl carbonyl. The difference between paths a and b is more complicated. In the enolic mechanism we have invoked, enol **4**, having the extended conjugation of the ester carbonyl, could be expected to predominate. In addition, molecular models show the acetyl group of **6** to present slightly less hindrance to attack. Both of these considerations favor path a, and this prediction is borne out experimentally.

Our next objective was to investigate the results of changing the steric and electronic situation by varying R in the starting β-keto ester. In this case, since two chemically different pyrroles were to be produced, evi-

(1) (a) Supported in part by Grant AI-04888 from the National Institutes of Health, U. S. Public Health Service; (b) National Institutes of Health Predoctoral Fellow.

(2) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958). In this paper it is recognized for the first time that use of a 3-alkyl-2,4-pentanedione, rather than acetylacetone itself, with the oximino-β-keto ester **1** causes the condensation to take a completely different course. The former gives a 2,4-dimethylpyrrole analogous to **9**, while the latter gives the normal Knorr product, 4-acetyl-2-carbethoxy-3,5-dimethylpyrrole.

dence for the presence of **10** was sought by direct mass spectral analysis of the crude pyrrolic product.

The investigation to test steric factors used the oximino derivative of ethyl pivaloylacetate [**1**, R = $C(CH_3)_3$] and β-diketone **2** (R′ = CH_3). Since the crude pyrrole, obtained in 46% yield, did not give peaks at *m/e* 295 (M^+), 280 ($M^+ - CH_3$), 222 ($M^+ - CH_2COOCH_3$), or 237 ($M^+ - CH_3 - CH_2COOCH_3$) even at high sensitivity, we concluded that path b (to form **10**) plays no role in this condensation.

If R should be an electron-donating moiety, it is possible that nucleophilic attack on the acyl group in **6** might be disfavored to a degree that appreciable reaction would proceed *via* path b, and **10** could be formed. To test this hypothesis, β-diketone **2** (R′ = CH_3) was condensed with the oximino derivative of ethyl anisoylacetate (**1**, R = *p*-$CH_3OC_6H_4$), giving a 40% yield of pyrrole. Through differential volatility, a mass spectrum of **10** (R = *p*-$CH_3OC_6H_4$, R′ = CH_3) was obtained: *m/e* 346 (7), 345 (M^+, 18), 300 (3), 299 (3), 276 (6), 226 (76), 198 (27), 135 (100). Preparative tlc afforded one band that contained pyrroles **9** (R′ = CH_3) and **10** (R = *p*-$CH_3OC_6H_4$, R′ = CH_3), based on mass spectral evidence; however, gas chromatography indicated that **10** was present in this fraction only in very minute amounts.

Apparently path b plays an increasing (although very small) part in the reaction as one varies R from $C(CH_3)_3$ through *p*-$CH_3OC_6H_4$ to CH_3. Molecular models show little steric difference between **4** and **5**, but there is slightly less steric hindrance to nucleophilic attack on the acyl group of **6** than on that of **7**. The increase in overall crowding with the bulkier R groups is reflected in lower yields of pyrrole and may accentuate differences between **6** and **7**, so that path b plays a smaller part than when R = CH_3. The electron-releasing properties of the anisyl group may hinder its irreversible loss as anisate from **6** enough so that path b is able to drain off some product as pyrrole **10**.

It appears that the major factor in determining which path will predominate is the enol distribution of the uncyclized intermediates **4** and **5**; the added stabilization that would accrue to **4** from the carbethoxy group should ensure its great predominance over **5** and hence would favor path a.

There has been a recent report[3] that modified Knorr condensation of **1** (R = CH_3) with 3-formyl-2-butanone gives two products: the expected (path a) 2,3-dimethyl-5-carbethoxypyrrole and also 2,3,4-trimethyl-5-carbethoxypyrrole resulting from path b. The 1,3-dicarbonyl system is certainly different from ours, but nonetheless it points to the reality of path b and indicates that proper choice of reactants could make it synthetically useful.

Experimental Section[4]

Methyl 4-Acetyl-5-oxohexanoate (2, R′ = CH_3).—Condensation of acetylacetone with methyl acrylate (2:1) using 1 mol of sodium ethoxide gave a 55–62% yield, but the product was contaminated with a small amount of the ethyl ester. Two procedures by Connor and McClellan[5] were tested: equimolar amounts of the above substrates were treated with 0.2 equiv of piperidine in one case, and 0.2 equiv of methoxide in the other. The latter gave 49% of the desired product, distilled through a 3-ft spinning-band column: bp 117–121° (5 mm) [lit.[6] bp 136.5° (11 mm)]; nmr (CCl_4) δ 2.12 (s), 3.61 (s), 2.4 (m).

Ethyl Pivaloylacetate.—This material was prepared according to the generalized procedure of Swamer and Hauser:[7] bp 83–85° (15 mm) [lit.[7] bp 96–100° (15 mm)]; nmr (CCl_4) δ 1.14 (s), 1.25 (t), 3.39 (s), 4.11 (q), 4.94 (s), 12.35 (s).

Ethyl Anisoylacetate.—The procedure used was similar to that of Wahl and Silberzweig.[8] Ethyl anisate (90.6 g, 0.50 mol) was heated at 140° while 15 g (0.65 g-atom, 30% excess) of sodium wire and 65.7 g (0.75 mol, 50% excess) of ethyl acetate (distilled from P_2O_5) were added in bits and drips, respectively, fresh sodium not being added until the previous had almost completely reacted. Addition was complete in 12 hr and the thick reddish-brown mixture was stirred at 115° for 2 days and then poured into 54 ml of concentrated HCl diluted with ice and water. The product was extracted into ether and washed with aqueous bicarbonate and water, the ether extracts were dried, and the ether was evaporated. *In vacuo* with the bath temperature below 130°, ethyl acetoacetate and ethyl anisate were distilled. The 100-ml residue was dissolved in ether, and the ether was washed with sodium carbonate solution and water and then dried. The residue obtained after evaporating the ether was vigorously shaken with saturated aqueous cupric acetate, adding aqueous potassium carbonate dropwise to neutralize the acetic acid produced. When the aqueous phase remained blue, it was removed from the dark green oil, and the green copper chelate was precipitated from the aqueous solution by adding ethanol, filtering, and washing with ethanol. Vacuum evaporation of the mother liquor and treatment again with cupric acetate gave a second crop of chelate, total yield 23.7 g (19%).

The β-keto ester was liberated by dissolving 9.5 g of the copper salt in 30 ml of glacial acetic acid, partitioning between ether and water, and washing the ether layer with saturated $NaHCO_3$ solution and water. After drying and removing the ether, the residue was distilled on a molecular still (0.06 mm, bath temperature 95°) to give the desired β-keto ester in 13% yield based on ethyl anisate added: nmr (CCl_4) δ 1.17 (t), 3.74 (s), 3.82 (s), 4.10 (q), 5.51 (s), 6.81 (d), 7.79 (d), 12.71 (s).

General Condensation Procedure.[9]—Into a 100-ml three-necked flask fitted with a dropping funnel and reflux condenser with nitrogen bubbler was introduced 75 mmol of the β-keto ester in 30 ml of glacial acetic acid. The contents were stirred and cooled in an ice bath as a solution of 5.90 g (86 mmol) of sodium nitrite in 20 ml of H_2O was added over 35 min. The mixture was stirred and cooled another 2 hr and then allowed to stand overnight.

To a 250-ml three-necked flask equipped as above was added 14.00 g (75 mmol) of methyl 4-acetyl-5-oxohexanoate in 35 ml of glacial acetic acid. The internal temperature was maintained at 65–80° while the previously prepared oxime solution was added over 1 hr 20 min, along with 12 g each of zinc dust and anhydrous sodium acetate in small portions. The mixture was stirred an additional 10 min and poured onto 400 g of ice. The precipitate was collected and dissolved in benzene, unreacted zinc was removed, and the benzene solution was evaporated to dryness.

The labeled pyrroles were recrystallized from methanol, benzene–hexane, and carbon tetrachloride, and then the specific activities were determined. The other pyrroles were dissolved in ether and washed with aqueous sodium carbonate, and the residue after evaporation was analyzed directly by mass spectroscopy.

2,4-Dimethyl-3-(β-carbomethoxyethyl)-5-carbethoxypyrrole: mp 103–104° (lit.[10] mp 104°); nmr ($CHCl_3$) δ 1.34 (t), 2.22 (s), 2.28 (s), 2.57 (m), 3.67 (s), 4.29 (q); $\nu_{max}^{CHCl_3}$ 1685, 1710, 1745 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 281 nm.

(3) M. W. Roomi and S. F. MacDonald, *Can. J. Chem.*, **48**, 1689 (1970).

(4) Specific activities were determined on a Nuclear Chicago Mark I scintillation counter; all samples were counted for at least 200 min. Mass spectra were determined by direct inlet on a Varian M-66 and on a Consolidated Electrodynamics Corp. Type 21, 103-C, instrument. Nmr spectra were measured on Varian A-60 and T-60 spectrometers. Gas chromatography was accomplished with an Aerograph A-700 instrument using a 2-ft 10% QF-1 on Chromosorb W column at 183°. Preparative tlc was done on a 1000-μ layer of Kieselgel D-5.

(5) R. Connor and W. R. McClellan, *J. Org. Chem.*, **3**, 570 (1939).

(6) R. Bertocchio and J. Dreux, *Bull. Soc. Chim. Fr.*, 823 (1962).

(7) F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 1352 (1950).

(8) A. Wahl and C. Silberzweig, *Bull. Soc. Chim. Fr.*, **12**, 25 (1912).

(9) A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc. C*, 2045 (1967).

(10) H. Fisher, O. Süs, and F. G. Weilguny, *Justus Liebigs Ann. Chem.*, **481**, 169 (1930).

2,4-Dimethyl-3-(β-carbomethoxyethyl)-5-carbobenzoxypyrrole: mp 99–100° (lit.[11] mp 99–100°); nmr (CCl_4) δ 2.15 (s), 2.25 (s), 2.48 (m), 3.56 (s), 5.23 (s), 7.27 (s); $\nu_{max}^{CHCl_3}$ 1680, 1730 cm^{-1}; $\lambda_{max}^{CH_3CH}$ 283 nm.

Registry No.—1 (R = CH_3), 5408-04-8; 1 (R = $C(CH_3)_3$), 27332-07-6; 1 (R = *p*-$CH_3OC_6H_4$), 27331-97-1; 2 (R′ = CH_3), 13984-53-7; benzyl 2-oximinoacetoacetate, 27331-98-2.

(11) A. Hayes, G. W. Kenner, and N. R. Williams, *J. Chem. Soc.*, 3779 (1958).

Synthesis of *endo*-4-Bromo-6-thiabicyclo[3.2.1]octane and 6-Thiabicyclo[3.2.1]oct-3-ene[1]

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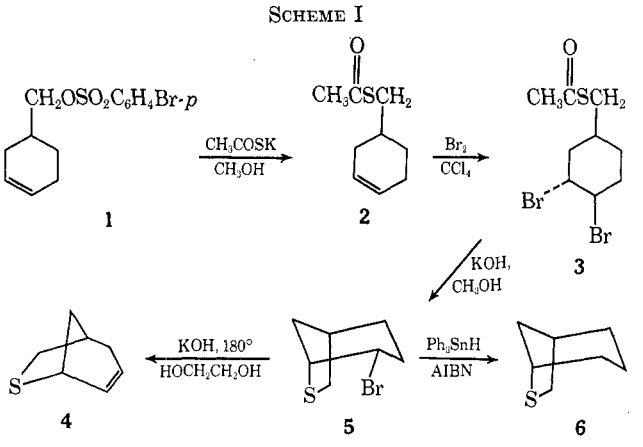
As part of a continuing program of investigation of stereochemical aspects of cyclic and bicyclic sulfur compounds, we have developed syntheses of *endo*-4-bromo-6-thiabicyclo[3.2.1]octane (**5**) and 6-thiabicyclo[3.2.1]-oct-3-ene (**4**). The synthetic sequences beginning with 3-cyclohexenylmethyl *p*-bromobenzenesulfonate (**1**) are summarized in Scheme I. Compound **1** was prepared by the sodium borohydride reduction of 3-cyclohexenecarboxaldehyde, followed by reaction of the alcohol with *p*-bromobenzenesulfonyl chloride in pyridine.

SCHEME I

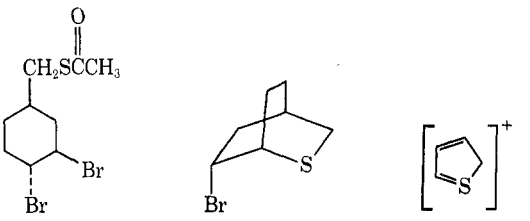


1 2 3 4 5 6

The critical step in Scheme I was the bromination of the thioacetate **2**. Trans-diaxial bromination[2] could give dibromide **3** and/or **7** depending on relative conformer populations and rates of bromination. Release of the nucleophilic thiolate by treatment of the dibromothioacetate with potassium hydroxide in methanol gave bicyclic bromide **5** in 62% yield. No material which could be identified as bromide **8** was found in the reaction product; either the bromination of **2** gave exclusively **3** or dibromothioacetate **7** failed to cyclize under the reaction conditions.

(1) Part XXVII in the series, "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 8648).

(2) K. Kozima, K. Sakashita, and S. Maeda, *J. Amer. Chem. Soc.*, **76**, 1965 (1954).



7 8 9

The structure of **5** was established by chemical and physical methods. Treatment of **5** with triphenyltin hydride[3] and azobisisobutyronitrile gave 6-thiabicyclo-[3.2.1]octane (**6**), identical by infrared spectroscopy[4] with that prepared by Birch and coworkers.[5] It was significant to note that the infrared spectrum of **5** was very similar to that of **6** in the 1050–650 cm^{-1} region suggesting that rearrangement did not occur during the reduction step.

The base peak in the mass spectrum of **5** was found at *m/e* 85. We suggest that this peak is indicative of the presence of a five-membered ring[6] and corresponds to ion **9**. The nmr spectrum of **5** revealed an eight-line pattern centered at δ 4.22 with coupling constants of 12, 6, and 2 Hz. This multiplet is assigned to the axial hydrogen at C-4 with the 12-Hz coupling constant due to trans-diaxial coupling.

The dipole moment of **5** in benzene solution was found to be 3.51 D. From models and model compounds the predicted dipole moment of **5** is 3.7 D (chair conformation) or 3.8 D (boat conformation). The isomeric *exo*-4-bromo-6-thiabicyclo[3.2.1]octane would be expected to have a dipole moment of 1.0 D (chair conformation) or 2.8 D (boat conformation).

The bicyclic bromide **5** was significantly unreactive. The common methods for achieving elimination, displacement, and solvolytic reactions on secondary bromides were unsuccessful. The sodium iodide in acetone test was negative after 23 hr at reflux.[7] The bromide **5** was recovered after 2 days in refluxing acetic acid, after 4 days in refluxing *tert*-butyl alcohol containing 10 equiv of potassium *tert*-butoxide, and after attempts to make lithium and Grignard reagents. The lack of success in these and similar reactions can probably be attributed to the close proximity of the sulfur to the departing bromide. SN1, SN2, and elimination reactions all involve a planar or developing planar transition state at C-4. Models of such a transition state reveal severe steric crowding between the departing bromine and the sulfur.

Two reactions of bromide **5** were successful. The first of these, triphenyltin hydride reduction, has been mentioned above. Dehydrobromination to yield 40% of 6-thiabicyclo[3.2.1]oct-3-ene (**4**) was achieved using potassium hydroxide in ethylene glycol at 180° for 18 hr. The nmr of **4** revealed two vinyl hydrogens. One was a broadened doublet centered near δ 5.4. The second was a broadened triplet pattern centered near δ 6.1. The pattern exhibited by these vinyl hydrogens was remarkedly similar to that observed in the vinyl region of

(3) E. J. Kupchik and R. E. Connolly, *J. Org. Chem.*, **26**, 4747 (1961).

(4) API Research Project 44 Catalog, in No. 1861.

(5) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **22**, 1590 (1957).

(6) The mass spectra of a number of bicyclic sulfides will be discussed in detail in a future paper.

(7) For another example of a bicyclic sulfur compound which failed to respond to this test, see E. D. Weil, K. J. Smith, and R. J. Gniber, *J. Org. Chem.*, **31**, 1669 (1966).