Condensation Cyclization Reactions of Electron-Deficient Aromatics. IV. Tricyclic Nitropropene Nitronates from the Reaction of Phloroglucinol and Cycloalkanones with *sym*-Trinitrobenzene

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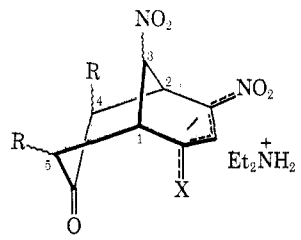
Interesting similarities have been shown between the reactions of *sym*-trinitrobenzene with cycloalkanones and with phloroglucinol. Previously unsuspected common intermediates have been shown to intervene. The structurally similar products in each case are tricyclic nitropropene nitronates. Protonation of these yields the corresponding nitronic acids in certain instances.

The reaction of simple acyclic ketones with electron-deficient aromatics in the presence of secondary amines has been shown to yield an interesting new type of bicyclic anion, **1**.[1,2] Acidification of such species (X = NO_2) many times gives a polymeric material, making it difficult to characterize the previously unreported nitropropene nitronic acids which might be expected to result. Because acidification of an alkaline mixture of phloroglucinol and *sym*-trinitrobenzene (TNB) was reported to yield a neutral compound, **2**,



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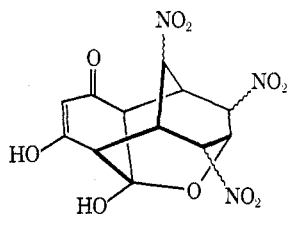

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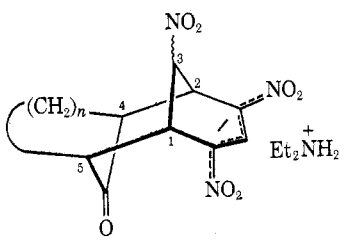
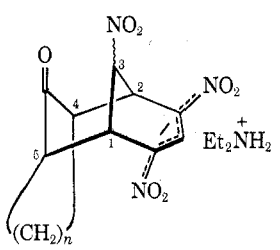
which closely resembles the type of compound which might be expected from the acidification of **1** (X = NO_2),[3,4] and because phloroglucinol can formally be considered a cyclic triketone which could condense with TNB in a manner analogous to simple ketones,[1,2] it was of interest to study the reaction of monocyclic ketones with TNB. The symmetry of the anticipated products, **3** or **4**, was expected to simplify pmr structural analysis



3a, $n = 2$
b, $n = 3$
c, $n = 4$



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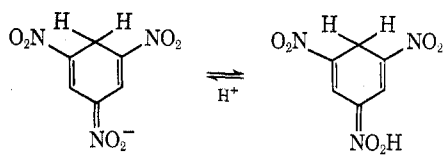
(previously made difficult by possible configurational isomerism at C-4 and C-5 of **1**), and we supposed that the rigid tricyclic structure of **3**, if formed, might be favorable for intramolecular cyclization to a structure analogous to **2**. In addition, it was of interest to reinvestigate the reaction of phloroglucinol and TNB to see whether the anionic precursor to **2** could be isolated.

We report here some interesting and previously unsuspected similarities between the phloroglucinol and simple cyclic ketone reactions, as well as a structural and chemical characterization of the tricyclic nitropropene nitronates **3b**, **3c**, and **9**, as well as the protonated forms (nitronic acids) of **3b** and **9**. These latter nitronic acids are the first examples of protonated nitropropene nitronates in the bicyclic series[1,2] to be characterized, and their properties relative to the nitronic acids, **6**, formed from protonation of 2,4,6-



5 **6**

trinitrocyclohexadienate σ complexes, **5**, are of considerable interest.[5]

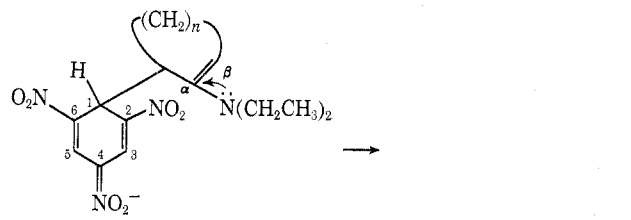
Addition of excess diethylamine to a solution of TNB in an excess of cyclohexanone results in an exothermic reaction which yields an intensely colored solution. The visible spectrum of this mixture exhibits the double maxima characteristic of anionic σ complexes, **5**.[6] The double maxima rapidly disappears as a single new maximum develops at 500 nm, characteristic of the nitropropene nitronate function of **1** (X = NO_2). Isosbestic points are observed at 470 and 570 nm. On standing for 24 hr at ambient temperature, crystals of product precipitate from solution. Recrystallization (see Experimental Section) yields bright red crystals, mp 225°, which analyze correctly for a 1:1:1 adduct of amine, TNB, and cyclohexanone. The 100-MHz pmr spectrum and ir spectrum of this product, when compared with pmr and ir spectra of bicyclic anions formed from acyclic ketones and TNB,[1,2,6] provide substantial evidence for structure **3b**. An alternate structure, **4**, in which the C-6 keto bridge is cis to the C-3 $CHNO_2$ bridge, is ruled out by the $J_{1,5}$ ($J_{2,4}$) coupling constant of 2.5 cps. The H-1–H-5

(1) M. J. Strauss and H. Schran, *J. Org. Chem.*, **36**, 856 (1971).
(2) M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Conner, *ibid.*, **35**, 383 (1970).
(3) T. Severin, *Chem. Ber.*, **90**, 2898 (1957).
(4) T. Severin and M. Bohn, *ibid.*, **100**, 211 (1967).
(5) C. Moberg and O. Wennerstrom, *Acta Chem. Scand.*, **25**, 2355 (1971); L. B. Clapp, H. Lacey, G. G. Beckwith, R. M. Srivastava, and N. Muhammed, *J. Org. Chem.*, **33**, 4262 (1968).
(6) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

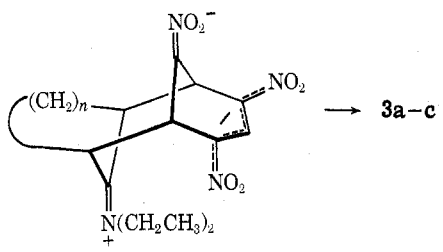
(H-2–H-4) dihedral angle in **3b** results in the observed value of 2.5 cps, whereas that in a structure like **4** would be about 8 cps. This result is not entirely unexpected, since **4** (n = 3) should be less thermodynamically stable. The relative thermodynamic stability of **3** and **4** would influence the type of product isolated only if equilibration is complete, however.

The configuration of C-3 in **3b** cannot be unambiguously established. We have provided some evidence that H-3 in **1** (X = NO_2; R = H) is directed toward the keto bridge.[7] In a series of anions like **1**,[1,2,7] the chemical shift of H-3 is always between δ 5.0 and 5.9, whereas in **3b** it is 6.2. The direction of this shift is not directly explicable.

The structure of **3b**, coupled with the previously proposed mechanism of secondary amine–acyclic ketone condensations with TNB[1] and the spectral changes occurring in the TNB–diethylamine–cyclohexanone reaction mixture (see Experimental Section), allow, us to propose a reasonable mechanistic route to the tricyclic product through the enamine σ complex **7b**. This latter type of complex likely forms from *in situ* generated enamine and TNB. Our recently reported kinetic study of a related sequence involving tertiary amines supports the intermediacy of tricyclic structures like **8**.[7]



7a, $n = 2$
b, $n = 3$
c, $n = 4$



8a, $n = 2$
b, $n = 3$
c, $n = 4$

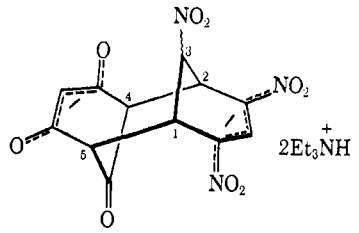
The reaction of cycloheptanone with TNB and diethylamine yielded the tricyclic anion **3c**. The reaction proceeded less rapidly than with cyclohexanone, and purification of the product by column chromatography was necessary. The pmr spectrum was essentially identical with that of **3b**, except for the added upfield methylene absorptions. The stereochemistry of the bridge cannot unambiguously be established, as the H-1 and H-5 (H-2 and H-4) protons are not well resolved and the $J_{1,5}$ ($J_{2,4}$) coupling constant could not be determined.

When an analogous reaction was attempted with cyclopentanone, the corresponding tricyclic anion **3a** could not be isolated. Although a small absorption at 500 nm (characteristic of the nitropropene nitronate function in **1**) was apparent in the visible spectrum of the reaction mixture, its rate of development was several orders of magnitude less than that which developed during formation of **3b**. Tlc of the cyclopentanone reaction mixture provided evidence for several products. These exhibited double maxima in their visible spectra, and are probably anionic σ complexes formed by attack of *in situ* generated enamine, cyclopentanoate anion, and diethylamine on TNB. It seems apparent that cyclization of **7a** is unfavorable relative to cyclization of **7b**, and that the reaction terminates at the σ complex stage. Drieding models clearly show that the distance between C-3 (C-5) and C-β in **7a** is almost 50% greater than in **7b**, when both intermediates are in the most favorable conformation for intramolecular cyclization. This results primarily from the rigidity of the cyclopentene ring in **7a**.

It is interesting to note that Severin has reported the tetracyclic structure **2**, which closely resembles **3**, as resulting from acidification of an alkaline solution of phloroglucinol and TNB.[4] Since tautomeric ketonic structures can be written for phloroglucinol, the possibility for a mechanistic route to the anionic precursor of **2** proceeding through anionic σ complex intermediates seems likely. We have reacted equivalent amounts of phloroglucinol and TNB in DMSO solution with excess diethylamine. The same visible spectral behavior of the reaction mixture is observed as in the reactions leading to **3b** and **3c**, except that the changes occur at a much more rapid rate. After several minutes, the spectrum of the reaction mixture consists of a single maximum at 500 nm, characteristic of the nitropropene nitronate function. A red powder can be obtained upon work-up of the reaction mixture (Experimental Section). This material contains a minimum of five compounds (tlc). Attempts at isolating pure products by chromatographic methods were unsuccessful. A similar diversity of products has been shown to arise from the reaction of diethylamine, acetone, and TNB.[8] The reaction was then carried out with triethylamine, since we supposed that the acidity of phloroglucinol would be sufficient so that a carbanionic mechanism for nitronate formation could occur. It is known that for nonacidic ketones, *i.e.*, acetone, diethylketone, and cyclohexanone, secondary amines must be employed to effect condensation–cyclization reactions with electron-deficient aromatics through enamine and immonium intermediates.[9,10] For more acidic ketones, *i.e.*, acetylacetone or dibenzyl ketone, tertiary amines will effect such reactions through carbanionic rather than enamine intermediates. The reaction of phloroglucinol, triethylamine, and TNB gave good yields of a single product which analyzed correctly for a 1:2:1 adduct of phloroglucinol, amine, and TNB. The pmr spectrum of this adduct is in accord with structure **9**. The $J_{1,5}$ coupling constant is less than 3 cps. Structure **10** should be much less stable due to repulsion of the two charge-delocalized functions. Structure **9** could quite possibly be a precursor to the tetracyclic structure **2**, isolated by Severin upon treating a mixture of TNB, potassium

(7) M. J. Strauss and H. Schran, *Tetrahedron Lett.*, 2349 (1971).

(8) R. Foster and C. A. Fyfe, *Tetrahedron*, **22**, 1831 (1966).
(9) M. J. Strauss and H. Schran, *J. Amer. Chem. Soc.*, **91**, 3974 (1969).
(10) M. J. Strauss and H. Schran, *J. Org. Chem.*, **36**, 856 (1971).



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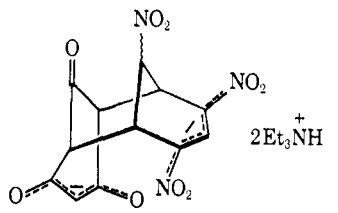

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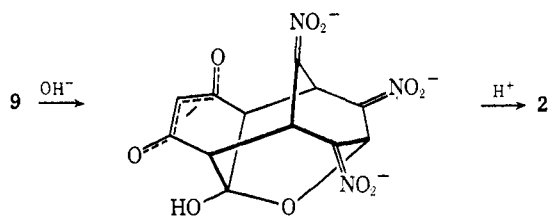
hydroxide, and phloroglucinol with 60% sulfuric acid.[4] Formation of the tetraanion **11** as an unstable inter-



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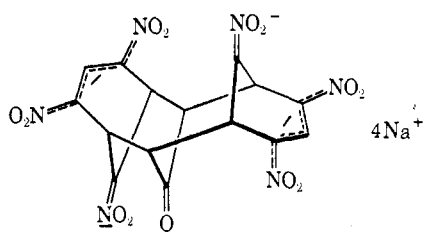
mediate preceding protonation is quite reasonable, since the structurally similar and isolable tetraanion **12**



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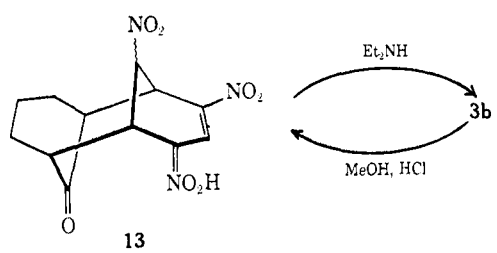
has previously been characterized.[11] All our attempts to isolate **2** by basification followed by acidification of **9** were unsuccessful. A variety of different procedures were attempted (see Experimental Section).

Although we have previously had some difficulty in isolating the nitronic acids of the bicyclic nitropropene anions **1**, we thought it essential to do so in the case of the structurally symmetric **3b** in order to compare the pmr spectral properties of the anion with those of the acid and **2**. After many failures we found that, by very carefully acidifying a methanol solution of **3b** with concentrated HCl at 15°, crystals of the nitronic acid **13** were formed after 24 hr. These analyzed



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(11) K. Kohasi, Y. Ohkura, and T. Momose, *Chem. Pharm. Bull.*, **19**, 213 (1971).

correctly for the expected acid and were readily converted back to the crystalline salt **3b** by treatment with diethylamine. The pmr spectrum of **13** and **3b** are quite similar, except for a few significant changes. Since the olefinic proton is a sharp singlet in **13**, protonation must have occurred on nitronate oxygen. There are no absorptions for the triethylammonium cation. The strong carbonyl band at 1710 cm^{-1} in the infrared spectrum of **13** appears at the same frequency as that in **3b**, clearly showing that cyclization to a structure analogous to **2** has not occurred.

By a similar acidification of **9** with methanolic HCl solution (anhydrous), yellow crystals of an acidic compound were obtained. These were extremely hygroscopic and unstable, and a satisfactory pmr spectrum and elemental analysis could not be obtained. The material could be the hydroxy endone nitronic acid of **9**, or the corresponding methyl enolate or nitronate. Upon standing in the atmosphere the surface of these crystals turn orange, and in aqueous solution a strong absorption at 500 nm rapidly develops, characteristic of the nitropropene nitronate function of **9**. Interestingly, treatment of the crystals with triethylamine yields a red powder, which after recrystallization is identical in all respects with the original salt **9**.

Experimental Section

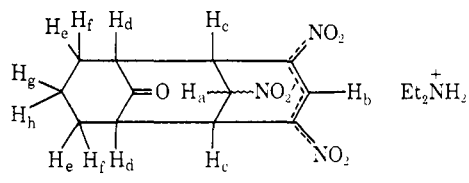
All melting points are uncorrected. Ir and uv spectra were recorded with Perkin-Elmer Model 21 and Model 402 spectrophotometers, respectively. Pmr spectra were recorded with JEOL MH-100 and PS-100 spectrometers, and chemical shifts are reported with respect to internal tetramethylsilane. Elemental analyses were performed by G. I. Robertson Laboratory, Florham Park, N. J.

Reaction of Cyclohexanone, Diethylamine, and TNB.—*sym*-TNB (2.0 g, 0.094 mol) was dissolved in a minimum amount of cyclohexanone at 40°. Diethylamine (2 ml) was then added, and the resulting exothermic reaction was moderated in a water bath at 15° (caution should be exercised with large-scale preparations). After standing for 24 hr, crystalline product is sometimes deposited from the reaction solution. If no crystals are deposited the reaction mixture can be washed with anhydrous diethyl ether until the oily residue is transformed to a red powder. Recrystallization from a 1:2 methanol–ether mixture yields red crystals of **3b** (*ca.* 30% yield), mp 225–226°. These analyzed correctly for a 1:1:1 adduct.

Anal. Calcd for $C_{16}H_{24}N_4O_7$: C, 50.11; H, 6.30; N, 14.61. Found: C, 50.27; H, 6.42; N, 14.80.

A methanolic solution of **3b** shows intense absorption at 510 nm, characteristic of the nitropropene nitronate function.

Since **3b** is the first tricyclic nitropropene nitronate isolated, and since its symmetry allows a detailed interpretation of the pmr spectrum, a complete analysis of the latter is included here (DMSO-d_6).



3b

Proton	Chemical shifts (δ) and splittings
H_a	1 H (t, J = 2.5 cps) 6.30; irrad H_c (s)
H_b	1 H (s) 8.21
H_c	2 H (m) 4.30; irrad H_d or H_a (d, J = 2.5 cps)
H_d	2 H (m) 2.58; irrad H_c (sharp m)
H_e, H_f	4 H (m) 2.2
H_g, H_h	1 H (m) 1.8; 1 H (m) 1.35
Cation	6 H (t) 1.1; 4 H (q) 3.0; 2 H (br) 6.6

The ir spectrum of **3b** (KBr) shows absorptions at 2860, 1730, 1550, 1460, 1378, 1265, 880, 778, and 753 cm^{-1}.

Protonation of 3b.—A saturated solution of **3b** in methanol at 25° was prepared under dry nitrogen and cooled to 10°. Concentrated HCl was then added until the orange color of **3b** disappeared. Cooling the resulting yellow solution for 24 hr at 10° resulted in the formation of yellow needles of the nitronic acid **13** (*ca.* 40%), mp 165°.

Anal. Calcd for $C_{12}H_{13}N_3O_7$: C, 46.35; H, 4.22; N, 13.50. Found: C, 46.10; H, 4.27; N, 13.42.

Addition of diethylamine to **13** yields a red powder, which when recrystallized from methanol–ether solution gave red crystals of **3b**, mp 226°, with spectral properties identical with those of the originally prepared salt. In all hydrolytic solvents, **13** dissociates to yield solutions having an intense absorption at 510 nm.

The pmr spectrum of **13** (acetone-d_6) is quite similar to that of **3b**, except for the absence of the cationic absorptions in the latter: δ7.86 ($CH{=}CNO_2H$, s), 6.42 ($CHNO_2$, t), 4.55 (NO_2H, s, exchange rapid with H_2O present in small quantities), 4.40 (2 H, bridgehead α to NO_2, m), 2.71 (2 H, bridgehead α to carbonyl, m), 2.41 (4 H, methylene, m), and 1.70 (2 H, methylene, m). The ir (KBr) of **13** shows absorptions at 1725, 1647, 1610, 1558, 1525, 1315, 1070, 905, and 778 cm^{-1}.

Reaction of Cycloheptanone, Diethylamine, and TNB.—*sym*-TNB (1.0 g, 0.047 mol) was dissolved in a minimum amount of cycloheptanone at 40°. Diethylamine (2 ml) was then added. After standing at room temperature for 3 weeks the total reaction mixture was chromatographed on a neutral silica gel column (15 × 0.75 in.) with THF containing 0.1% diethylamine. Various eluent fractions were evaporated down and the resulting oils were chromatographed by tlc (silica gel). Those fractions containing a single component (major product) were combined, and the resulting material was recrystallized from a 1:3 methanol–ether solution to give bright red crystals of **3c**, mp 215°. This product had an intense visible absorption at 510 nm in methanol solution, and analyzed correctly for the expected 1:1:1 adduct. The carbon analysis was not within the standard limit of ±0.3%, as the material was difficult to dry.

Anal. Calcd for $C_{17}H_{26}N_4O_7$: C, 51.25; H, 6.58; N, 14.06. Found: C, 50.69; H, 6.81; N, 13.81.

The nmr spectrum (DMSO-d_6) of **3c** was quite similar to that of **3b**, except for additional upfield methylene absorptions: δ 8.18 ($O_2NC{=}CHC{=}NO_2$, s), 5.8 ($CHNO_2$, t), 4.02 (2 H, bridgehead α to NO_2, m), 2.72 (2 H, bridgehead α to carbonyl, m), 2.0–1.5 (8 H, methylenes, br), 1.15 (6 H, $CH_3CH_2NH_2^+$, t), and 2.9 (4 H, $CH_3CH_2NH_2^+$, q).

The ir spectrum of **3c** (KBr) shows absorptions at 1718, 1630, 1560, 1425, 1377, 1260, 887, 726, and 745 cm^{-1}.

Reaction of Cyclopentanone, Diethylamine, and TNB.—Attempts to prepare the bicyclic adduct **3a** by methods similar to those described for **3b** and **3c** were unsuccessful. Tlc of the reaction mixture after 2 hr or after 2 weeks showed more than four major products.

Reaction of Phloroglucinol, Diethylamine, and TNB.—Although the visible spectrum of a mixture of phloroglucinol, TNB, and diethylamine does show evidence for initial formation of a σ complex, followed by cyclization to the bicyclic nitropropene nitronate, no crystalline product could be obtained from this reaction. The *in situ* generated enamine of diethylamine and phloroglucinol must be of considerably different reactivity from those of simple cyclic ketones, since a variety of products is observed to form (tlc).

Reaction of Phloroglucinol, Triethylamine, and TNB.—*sym*-TNB (1.0 g, 0.047 mol) and phloroglucinol·$2H_2O$ (1.0 g, 0.061 mol) were dissolved in a mixture of 4 ml of THF and 1 ml of DMF. To this mixture 3 ml of triethylamine were slowly added and the mixture was cooled to 10–15°. After 1 hr, the reaction mixture was triturated with four 50-ml portions of anhydrous ether. After the ether was decanted, the remaining insoluble oil was recrystallized from a 1:3 methanol–ether solution to yield orange crystals (*ca.* 50%), mp 123–124°, which analyze correctly for **9**.

Anal. Calcd for $C_{24}H_{39}N_5O_9$: C, 53.20; H, 7.25; N, 12.98. Found: C, 53.11; H, 7.62; N, 12.91.

The pmr spectrum of **9** (DMSO-d_6) shows absorptions at δ 8.1 ($O_2NC{=}CHC{=}NO_2$, s), 5.9 [2 H, $(CH_3CH_2)_3N^+H$, br], 5.6 ($CHNO_2$, t), 5.0 ($O{-}C{=}CHC{=}O$, s), 4.17 (2 H, bridgehead α to NO_2, m), 3.08 [12 H, $(CH_3CH_2)_3N^+H$, q], 2.93 (2 H, bridgehead α to carbonyl, d), and 1.15 [18 H, $(CH_3CH_2)_3N^+H$, t]. The ir spectrum of **9** (KBr) shows absorptions at 1720, 1550, 1520, 1235, and 1225 cm^{-1}. The electronic spectrum shows two intense peaks of equal intensity at 510 and 272 nm (MeOH). The latter absorption undoubtedly arises from the hydroxy enolate anion function in **9**, as it is not observed in **3b** or **3c**.

Registry No.—**3b**, 35740-40-0; **3c**, 35740-41-1; **9**, 35725-76-9; **13**, 35740-42-2; cyclohexanone, 108-93-0; TNB, 99-35-4; cycloheptanone, 502-42-1; phloroglucinol, 108-73-6.

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