of 1-carbethoxy-5-(γ-hydroxypropyl)-3-azapyrrocoline as a pale yellow oil. This was dissolved in a mixture of 150 ml of methanol and 40 ml of a 10% aqueous potassium hydroxide solution and allowed to stand at room temperature for 14 hr. After removal of the methanol, the residue was taken up in water and acidified. The resulting precipitate was collected and recrystallized from benzene to give 2.53 g of white crystals: mp 160–161°; $\lambda_{max}^{Nujol}$ 2.98 μ (hydroxyl), 6.08 (carboxyl), 12.65 and 13.31 (aromatic CH); $\lambda_{max}^{EtOH}$ 305 mμ (ε 12,200), 239 (8880), 222 (35,500), and 218 (shoulder).

*Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.74; H, 5.66; N, 12.69.

**3,5-Trimethylen-3-azapyrrocolinium Iodide (X).**—A solution of 1.0 g of 1-carboxy-5-(γ-hydroxypropyl)-3-azapyrrocoline (VIIIc) in 25 ml of 57% hydriodic acid was boiled under reflux for 3 hr. After neutralization of the cold solution with aqueous potassium carbonate, the solution was extracted with four 70-ml portions of chloroform. When the chloroform extract was dried and concentrated, it yielded an oil soluble in organic solvents and, presumably, mainly the free base derived from IX. However, on standing at room temperature, this oil rapidly crystallized with the solid product having the properties to be expected for the ring-closed, ionic structure X. Recrystallization of this solid from ethanol gave 856 mg of white crystals: mp 320° dec; $\lambda_{max}^{Nujol}$ 6.18 and 12.61 μ; $\lambda_{max}^{EtOH}$ 307 mμ (ε 7300), 303 (7300), 292 (7450), 289 (5930), 222 (28,600), and 218 (42,900); nmr [deuterium oxide with 3-(trimethylsilyl)-1-propanesulfonic acid as internal standard] showed complex aromatic absorption between τ 1.52 and 3.46, a triplet (1 H) at 5.20, and the remaining aliphatic protons as a complex between 6.01 and 7.88.

*Anal.* Calcd for $C_{10}H_{11}N_2I$: C, 41.98; H, 3.86; N, 9.79. Found: C, 42.16; H, 4.16; N, 9.50.

**Registry No.**—VIa, 16205-44-0; VIb, 16205-45-1; VIIa, 16205-46-2; VIIb, 16205-47-3; VIIc, 16205-48-4; VIIIa, 274-56-6; VIIIb, 16205-50-8; X, 16205-51-9.

# The Behavior of 2-Halo- and 2-Trifluoromethyl-1,4-benzoquinones in the Nenitzescu Indole Synthesis

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*Received December 7, 1967*

The 2-halo-1,4-benzoquinones (**1**) usually react with ethyl 3-aminocrotonate (**2a**) to give mixtures of the ethyl 6- and 7-halo-5-hydroxy-2-methylindole-3-carboxylates; however, 2-fluoro-1,4-benzoquinone (**1c**) gives only the 6 isomer. 2-Trifluoromethyl-1,4-benzoquinone (**5**) reacts with **2a** and *t*-butyl 3-aminocrotonate (**2b**) to furnish good yields of the ethyl (**6a**) and *t*-butyl (**6b**) esters of 5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylic acid. The reactions of **2a** with 2-chloro-3-trifluoromethyl-1,4-benzoquinone (**9**), 2-chloro-5-trifluoromethyl-1,4-benzoquinone (**12**), and 2-methoxy-5-trifluoromethyl-1,4-benzoquinone (**15**) were also examined. The products isolated in each instance indicate that the inductive effect of the trifluoromethyl substituent largely determines the site of the initial carbon–carbon bond formation and, thus, the orientation of the benzene-ring substituents in the resulting 5-hydroxy-2-methylindole-3-carboxylates. The directive influence of this group in conjunction with its replacement by hydrogen on acid hydrolysis affords a route to difficulty accessible indoles, *e.g.*, the two-stage preparation of 7-chloro-2-methylindol-5-ol (**14**) from **12**. Decarbalkoxylation of *t*-butyl ester **6b** with *p*-toluenesulfonic acid gave 2-methyl-4-trifluoromethylindol-5-ol (**19a**). Lithium aluminum hydride reduction of 5-methoxy-2-methyl-4-trifluoromethylindole (**19b**) furnished 5-methoxy-2,4-dimethylindole (**20**).

The general utility of the Nenitzescu indole synthesis,[1] wherein a *p*-benzoquinone condenses with an alkyl 3-aminocrotonate, for the preparation of 5-hydroxyindole-3-carboxylates is well documented.[2] Although the mechanism[2,3] of this reaction suggests that a monosubstituted quinone could give 4-, 6-, and 7-substituted 5-hydroxyindole-3-carboxylates, the 6 isomer is most generally noted. However, it is apparent that the product distribution will be influenced by the steric nature and electronic character of the quinone substituent.[4] Steric forces may exert their influence in either of two ways. (1) Addition of the enamine to the quinone 5 or 6 position may be preferred over the adjacent 3 position. In fact, the lack of 4 isomer formation with alkylquinones[2,5] can be explained by this effect. (2) When enamine addition occurs at the 6 position, these forces may mitigate against the required subsequent nitrogen–carbon condensation. Thus, the observed quantity of 7 isomer declines precipitously by varying the quinone substituent from methyl to ethyl.[2] The electronic effect of the quinone substituent should influence the isomer distribution in a predictable manner. Thus, with 2-methoxy-1,4-benzoquinone,[2,6] the strong electron-donating methoxy group leads to enamine condensation at the 5 position.[7] On the other hand, substitution of benzoquinone with the electron-withdrawing carbomethoxy group results in condensation at the 3 position, with the subsequent formation of 4-carbomethoxy-5-hydroxyindole.[8] In this paper we describe our studies with quinones having electronegative substituents that might activate the 3 position by inductive effects.

The 2-halo-1,4-benzoquinones were of interest in this respect, inasmuch as the inductive effect of the substituent is opposed by a resonance effect. In fact, as a result of these opposing factors, the formation of a 4-substituted 5-hydroxyindole is not observed. Thus,

(1) C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

(2) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 2536 (1966).

(3) D. Raileanu and C. D. Nenitzescu, *Rev. Roumaine Chim.*, **10**, 339 (1965); *Chem. Abstr.*, **63**, 9903 (1965).

(4) H. S. Wilgus, III, E. Frauenglass, E. T. Jones, R. F. Porter, and J. W. Gates, Jr., *J. Org. Chem.* **29**, 594 (1964).

(5) S. A. Monti, *ibid.*, **31**, 2669 (1966).

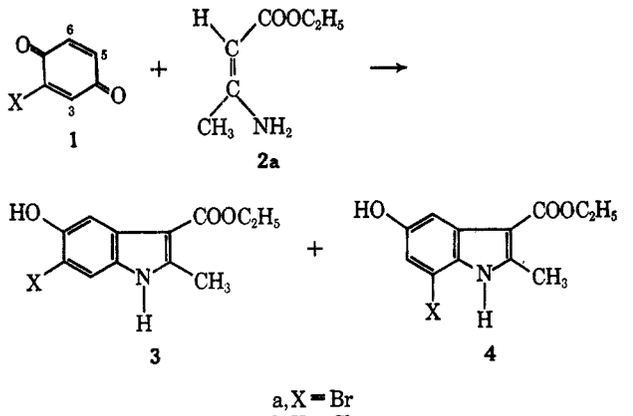
(6) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).

(7) The possibility that steric forces contribute to the exclusive formation of the 6-methoxy isomer (*cf.* 2-ethyl-1,4-benzoquinone) appears unlikely, inasmuch as nucleophilic reactions with 2-methoxy-1,4-benzoquinone lead to high yields of 5-substituted methoxyhydroquinones (see ref 4 for leading references).

(8) G. R. Allen, Jr., and M. J. Weiss, *J. Org. Chem.*, **33**, 198 (1968).

2-bromo- (**1a**), 2-chloro- (**1b**), and 2-iodo-1,4-benzoquinone (**1d**) react with ethyl 3-aminocrotonate (**2a**) to give mixtures of the 6- (**3**) and 7-substituted (**4**) isomers (see Scheme I),[9] and in the instance of 2-fluoro-1,4-

SCHEME I

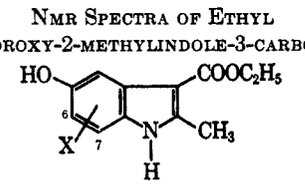


a, X = Br
b, X = Cl
c, X = F
d, X = I

benzoquinone (**1c**) only the 6 isomer (**3c**) was observed. The indoles **3** and **4** exhibited the expected triad ($\lambda_{max}$ 214–217, 243–248, 284–300 m$\mu$) in their ultraviolet spectra, and their common structural features were indicated by the consistent pattern of the nmr spectra. Thus, ethoxyl ($\delta$ 1.35–137, 4.26–4.30; $J$ = 7.5 cps), methyl ($\delta$ 2.60–2.67), hydroxyl ($\delta$ 9.21–9.67), and heteroatom proton resonances were observed in addition to the single aryl proton resonances given in Table I. The coupling patterns evident in these last resonances served to identify the products as the 6- or 7-substituted isomers. Low yields were noted in these condensations (see Table II), and partition chromatography was required for separation of the products. However, no effort was made to find optimum conditions.

TABLE I

NMR SPECTRA OF ETHYL HALO-5-HYDROXY-2-METHYLINDOLE-3-CARBOXYLATES



| Compound | X | δ Values of protons at positions[a] 4 | 6 | 7 |
|---|---|---|---|---|
| **3a** | 6-Br | 7.53 | | 7.45 |
| **4a** | 7-Br | 7.40[b] | 6.86[b] | |
| **3b** | 6-Cl | 7.59 | | 7.31 |
| **4b** | 7-Cl | 7.35[b] | 6.73[b] | |
| **3c** | 6-F | 7.56[c] | | 7.15[d] |
| **3d** | 6-I | 7.53 | | 7.65 |
| **4d** | 7-I | 7.40[b] | 7.05[b] | |

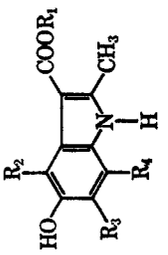
[a] Measured in dimethyl sulfoxide-$d_6$ and expressed as downfield shifts from an internal tetramethylsilane standard. [b] $J_{H_4-H_6}$ = 2.5–3.0 cps. [c] $J_{H_4-F}$ = 9.0 cps. [d] $J_{H_7-F}$ = 11.2 cps.

In contrast to the haloquinones, the substituent in 2-trifluoromethyl-1,4-benzoquinone (**5**) exerts only an

(9) The reaction of 2-chloro-1,4-benzoquinone (**1b**) with ethyl 3-aminocrotonate (**2a**) was reported previously to give a single isomer of undetermined structure: A. N. Grinev, N. K. Kul'bovskaya, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **25**, 1355 (1955); *Chem. Abstr.*, **50**, 4903 (1956).

TABLE II

SUBSTITUTED ALKYL 5-HYDROXY-2-METHYLINDOLE-3-CARBOXYLATES

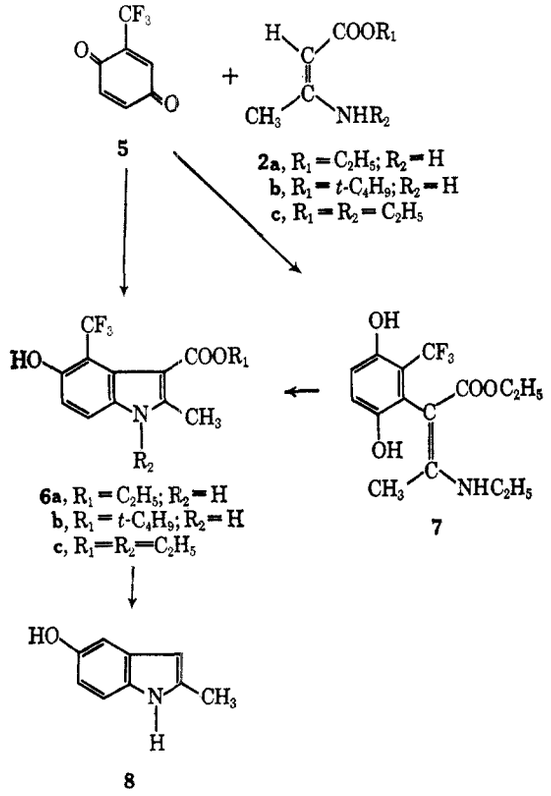


| Compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Chromatography: Solvent system[a] | Hbv | $V_m/V_s$ | Recrystn solvent | Mp, °C | Yield, % | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found | Fluorine, % Calcd | Fluorine, % Found | Other halogen, % Calcd | Other halogen, % Found | Nitrogen, % Calcd | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | $C_2H_5$ | H | Br | H | HEMW (75:25:15:6) | 5.0 | 2.4 | Acetone–hexane | 212d[b] dec | 5 | $C_{13}H_{12}BrNO_3 \cdot C_4H_8O^c$ | 49.91 | 49.89 | 4.80 | 4.84 | | | 23.72 | 22.94 | 4.17 | 3.75 |
| **3b** | $C_2H_5$ | H | Cl | H | HEMW (70:30:15:6) | 2.6 | 2.7 | Acetone–hexane | 216–217[d] | 20 | $C_{13}H_{12}ClNO_3$ | 56.81 | 57.23 | 4.77 | 5.16 | | | 13.98 | 14.51 | 5.52 | 4.90 |
| **3c** | $C_2H_5$ | H | F | H | HEMW (65:35:15:6) | 4.1 | 2.4 | Acetone–hexane | 191–192 dec | 12 | $C_{13}H_{12}FNO_3$ | 60.75 | 60.79 | 5.10 | 4.79 | 8.01 | 7.70 | | | 5.91 | 5.79 |
| **3d** | $C_2H_5$ | H | I | H | HEMW (80:20:15:6) | 4.9 | 2.5 | $CH_2Cl_2$–hexane | 201–202 dec | 1 | $C_{13}H_{12}INO_3$ | 41.76 | 41.87 | 3.51 | 3.53 | | | 36.78 | 36.65 | 4.06 | 3.98 |
| **4a** | $C_2H_5$ | H | H | Br | HEMW (75:25:15:6) | 3.9 | 2.4 | Acetone–hexane | 192–193 | 2 | $C_{13}H_{12}BrNO_3$ | 48.34 | 48.01 | 4.06 | 4.56 | | | 26.81 | | 4.70 | 4.75 |
| **4b** | $C_2H_5$ | H | H | Cl | HEMW (70:30:15:6) | 1.8 | 2.7 | Acetone–hexane | 199–200 dec | 4 | $C_{13}H_{12}ClNO_3$ | 56.81 | 56.91 | 4.77 | 5.09 | | | 13.98 | | 5.52 | 5.48 |
| **4d** | $C_2H_5$ | H | H | I | HEMW (80:20:15:6) | 4.3 | 2.5 | $CH_2Cl_2$–hexane | 201–203 dec | 7 | $C_{13}H_{12}INO_3$ | 41.76 | 41.90 | 3.51 | 3.62 | | | 36.78 | 35.88 | 4.06 | 3.94 |
| **6a** | $C_2H_5$ | $CF_3$ | H | H | | | | Acetone–hexane | 174–175 dec | 54 | $C_{14}H_{12}F_3NO_3$ | 54.36 | 54.34 | 4.21 | 3.86 | 19.84 | 19.96 | | | 4.88 | 4.96 |
| **6b** | $i$-$C_4H_9$ | $CF_3$ | H | H | | | | | 225–227 dec[e] | 62 | $C_{16}H_{16}F_3NO_3$ | 57.14 | 57.28 | 5.12 | 4.81 | 18.08 | 17.79 | | | 4.44 | 4.36 |
| **10** | $C_2H_5$ | H | Cl | $CF_3$ | | | | Benzene–heptane | 136–138 | 78 | $C_{14}H_{11}ClF_3NO_3$ | 48.54 | 48.53 | 3.45 | 3.45 | 17.72 | 17.45 | 11.02 | 11.04 | 4.36 | 4.24 |
| **13** | $C_2H_5$ | $CF_3$ | H | Cl | | | | Ether–hexane | 196–198 dec | 74 | $C_{14}H_{11}ClF_3NO_3$ | 48.54 | 48.34 | 3.45 | 3.54 | 17.72 | 17.35 | 11.02 | 11.72 | 4.36 | 4.22 |
| **16**[f] | $C_2H_5$ | $CF_3$ | H | $OCH_3$ | HEMW (70:30:15:6) | 3.4 | 2.6 | Acetone–hexane | 212–214 | 25 | $C_{14}H_{14}F_3NO_4$ | 53.00 | 52.82 | 4.45 | 4.57 | 17.96 | 17.97 | | | 4.43 | 4.58 |
| **17**[f] | $C_2H_5$ | $OCH_3$ | H | $CF_3$ | HEMW (70:30:15:6) | 7.1 | 2.6 | Acetone–hexane | 178–180 | 25 | $C_{14}H_{14}F_3NO_4$ | 53.00 | | 4.45 | | 17.96 | 17.86 | | | 4.43 | 4.55 |

[a] Solvents: H = heptane, E = ethyl acetate, M = methanol, W = water. [b] Identical by the usual criteria with material prepared by bromination of ethyl 5-hydroxy-2-methylindole-3-carboxylate: M. R. Bell, R. Oesterlin, A. L. Beyler, H. R. Harding, and G. O. Potts, *J. Med. Chem.*, **10**, 264 (1967). [c] Indicated in the nmr spectrum. [d] Grinev and coworkers[9] report mp 213° for their product from the reaction of **1c** and ethyl 3-aminocrotonate. [e] Purified by sublimation. [f] Assignments may be reversed with respect to $R_2$ and $R_4$ (see opening of article).

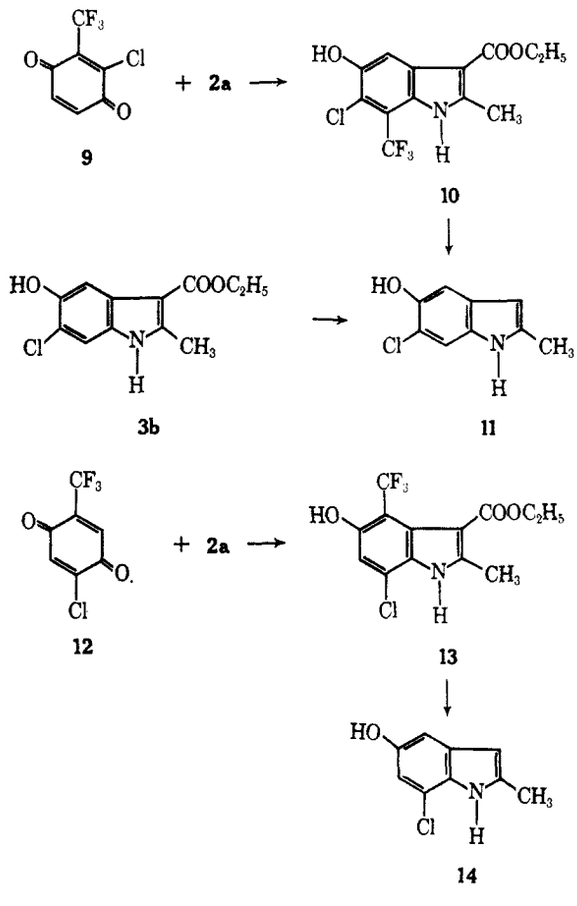
inductive effect.[10] In fact, our studies with this quinone indicate that this effect dominates any steric forces that mitigate against condensation at the 3 position (*cf.* toluquinone[2]). Thus, quinone **5** undergoes enamine addition exclusively at this site with the aminocrotonates **2a–c** (see Scheme II). The 4-trifluoromethylindoles **6a** and **6b** (54–62%) result directly with the N-unsubstituted crotonates **2a** and **2b**. The usual triad ($\lambda_{max}$ 218, 247, 302 mμ) in the ultraviolet spectra indicated the indolic character of these products, which was confirmed by acid treatment of **6a** to give the known[1,6] 2-methylindol-5-ol (**8**).[11,12] The coupling constant ($J$ = 8.5 cps) of the single proton resonances at δ 6.90 and 7.35 in the nmr spectra of **6a** and **6b** define them as the 4 isomers. In the instance of ethyl 3-ethylaminocrotonate (**2c**), for a reason that is not apparent, the enamine adduct **7** appears to have *trans* (ring–amine) stereochemistry,[13] and indole formation is not observed. However, completion of the indole synthesis to give **6c** (86%) could be effected by equilibration of **7** with acetic acid under oxidative conditions (presence of **5**). This transformation in conjunction with microanalytical and spectral data ($\lambda_{max}$ 292 mμ; single-proton resonances at δ 6.15 and 6.90, $J$ = 10 cps) serve to define the structure of **7**.

SCHEME II




In view of the specificity noted with quinone **5**, the behavior of certain substituted 2-trifluoromethyl-1,4-benzoquinones in the Nenitzescu condensation was also studied. When the second substituent is chlorine, the directive influence of the trifluoromethyl group dominates the reaction course. Thus, 2-chloro-3-trifluoromethyl-1,4-benzoquinone (**9**) reacts with ethyl 3-aminocrotonate (**2a**) to give the 6-chloro-7-trifluoromethylindole derivative **10** (78%) (see Scheme III). The pattern of nuclear substitution in this product was ascertained by treatment of **10** with 20% hydrochloric acid to give 6-chloro-2-methylindol-5-ol (**11**), identical with the decarbethoxylation product derived from the 6-chloro-5-hydroxyindole-3-carboxylate **3b**. Aminocrotonate **2a** reacts with 2-chloro-5-trifluoromethyl-1,4-benzoquinone (**12**) to furnish the 7-chloro-4-trifluoromethylindole **13**. The orientation of the substituents in this product was defined by hydrolytic conversion of **13** into 7-chloro-2-methylindol-5-ol (**14**), the nmr spectrum (δ 6.64 and 6.83, $J$ = 2.5 cps) of which requires two aryl protons in a *meta* relationship.

SCHEME III



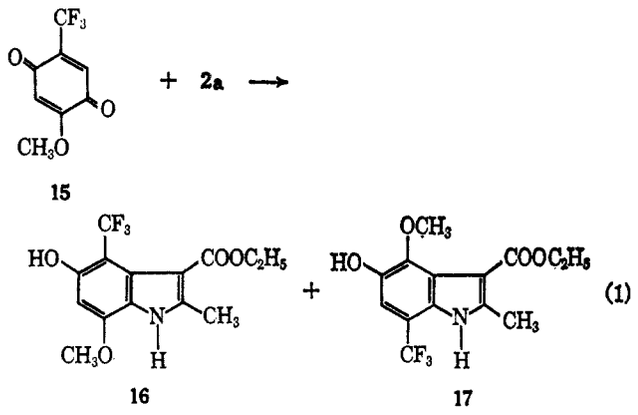

The directive influence of the trifluoromethyl group also competes with the strongly electron-donating methoxyl group, so that reaction of 2-methoxy-5-trifluoromethyl-1,4-benzoquinone (**15**) with aminocrotonate **2a** (eq 1) gives the two possible isomeric indoles **16** and **17** in equivalent yield (25% each). The orientation of the 4 and 7 substituents in these isomers could not be assigned with certainty. Efforts to remove the trifluoromethyl and ester functions by acid hydrolytic treatment gave unresolvable mixtures (tlc), presumably as a result of partial ether cleavage.

(10) (a) A. Steitwieser, Jr., and D. Holtz, *J. Amer. Chem. Soc.*, **89**, 692 (1967); (b) A. Streitwieser, Jr., A. P. Marchand, and A. H. Pudjaatmaka, *ibid.*, **89**, 693 (1967).

(11) The acid and alkaline hydrolytic conversion of certain benzotrifluorides into benzoic acids has been reported,[12a] as well as the hydrolytic removal of an aryl trifluoromethyl group.[12b]

(12) (a) W. B. Whalley, *J. Chem. Soc.*, 3016 (1949); (b) L. H. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, **28**, 3013 (1963).

(13) The vinyl methyl proton resonance for five such adducts[2,8] appears at δ 1.57–1.88. In the present instance the stereochemistry cannot be determined by this technique, for the vinyl methyl proton resonance (δ 2.25) is removed from the cited range and intermediate between that recorded for *cis* (ester–amine) (δ 1.78) and *trans*-ethyl 3-benzylaminocrotonate (δ 2.62): G. O. Dudek and G. P. Volpp, *J. Amer. Chem. Soc.*, **85**, 2697 (1963).



15 16 17 (1)

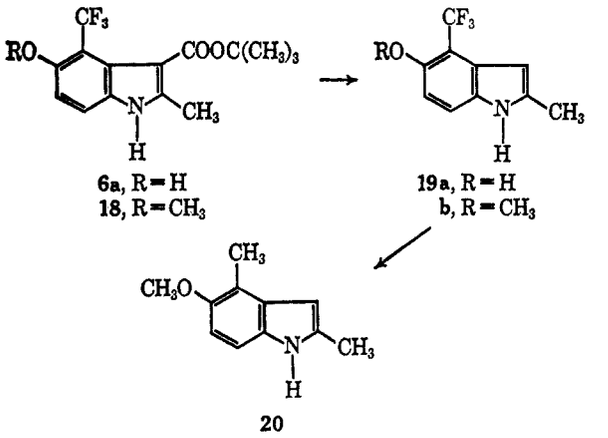
Tentative assignment of the 4-trifluoromethyl structure **16** to the isomer of mp 212–214° and the 7-trifluoromethyl structure **17** to that of mp 178–180° was suggested by the following nmr and infrared spectral comparisons. In the nmr spectra the 1-proton resonance of **17** appears 0.47 ppm downfield from that of 16; a similar downfield shift, but of smaller magnitude (0.28 ppm), for this resonance is observed in a comparison of the spectra of 6-chloro derivative **3b** and the 6-chloro-7-trifluoromethyl derivative **10**. These shifts suggest a possible deshielding effect by the 7-trifluoromethyl substituent. Moreover, small (0.067–0.092 ppm) downfield shifts in the ester and 2-methyl proton resonances for the higher melting isomer indicate a greater electronic interaction of these groups with the trifluoromethyl group; structure **16** would more reasonably account for such an effect. The position (5.95 $\mu$) of the carbonyl band in the infrared spectrum of **16** is in agreement with the position (5.90–5.94 $\mu$) observed for this absorption with the 4-trifluoromethylindole-3-carboxylates **6** and **13**, and represents a hypsochromic shift of 0.07 $\mu$ from the location of this band in the spectra of **17** and **10**. This shift would appear to be the result of a dipole–dipole interaction[14] or the electronic interaction of the trifluoromethyl group with the heteroatom.

We have illustrated above that the directive influence of the trifluoromethyl group in conjunction with its replacement by hydrogen on hydrolytic treatment allows the preparation of certain difficulty accessible indoles, *e.g.*, 7-chloro-2-methylindol-5-ol (**14b**). This group also affords other synthetic possibilities in the important 5-hydroxyindole series. In contrast to its concomitant removal in hydrolytic decarbalkoxylations, the trifluoromethyl group may be retained selectively through the utilization of *t*-butyl esters; thus **6b** and the derived methyl ether **18** furnish the 4-trifluoromethylindoles **19** on heating with *p*-toluenesulfonic acid (see Scheme IV). Finally, reduction of the trifluoromethyl group affords a method for the introduction of a methyl substituent, as demonstrated by the conversion of **19b** into **20** with lithium aluminum hydride.[15] It may be noted that 4-methyl-5-hydroxyindoles can not be prepared directly by the Nenitzescu condensation with toluquinone.

(14) (a) E. J. Corey, *J. Amer. Chem. Soc.*, **76**, 175 (1954); (b) G. R. Allen, Jr., L. J. Binovi, and M. J. Weiss, *J. Med. Chem.*, **10**, 7 (1967).

(15) Similar reductions of a benzotrifluoride [H. J. Brabander and W. B. Wright, Jr., *J. Org. Chem.*, **32**, 4053 (1967)] and a 6-trifluoromethylindole [A. Kalir, Z. Pelah, and D. Balderman, *Israel J. Chem.*, **5**, 101 (1967)] have been noted.

SCHEME IV



6a, R = H; 18, R = $CH_3$ 19a, R = H; b, R = $CH_3$ 20

## Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60 spectrometer in the indicated solvent using tetramethylsilane as an internal standard. Evaporations were carried out under reduced pressure. 2-Bromo- (**1a**),[16] 2-chloro- (**1b**),[17] 2-fluoro- (**1c**),[18a] and 2-iodo-1,4-benzoquinone (**1d**)[18b] were prepared as described in the literature.

**2-Trifluoromethyl-1,4-benzoquinone** (**5**).—A solution of 385 g (2.18 mol) of 2-amino-5-hydroxybenzotrifluoride[12a] in 3.9 l. of 20% $H_2SO_4$ was stirred vigorously with 6 l. of heptane for 3 hr while 670 g (2.25 mol) of $Na_2Cr_2O_7$ in 2 l. of water was added. During addition the mixture was maintained at less than 10° by external cooling. After completion of the addition, the reaction mixture was stirred in the cold for an additional 2 hr. The layers were separated and the aqueous layer was extracted three times with 2-l. portions of heptane. The organic layers were dried and cooled in a Dry Ice bath to give 125 g (33%) of **5**, mp 54–55° (lit.[19] mp 51–54°).

**2-Chloro-5 trifluoromethylhydroquinone.**—A solution of 76.5 g (0.32 mol) of sodium persulfate in 145 ml of water was added dropwise over 4.5 hr to a stirred solution of 62.8 g (0.32 mol) of 3-hydroxy-4-chlorobenzotrifluoride and 64.0 g (1.6 mol) of sodium hydroxide in 640 ml of water. The resulting solution was allowed to stand at ambient temperature for 5 days. The pH of the solution was rendered acid to congo red test paper by dropwise addition of concentrated hydrochloric acid solution. Extraction with ether gave 68% recovery of the phenol. The aqueous solution was treated with 20 ml of concentrated hydrochloric acid and 250 ml of ether. The mixture was heated under gentle reflux for 30 min. The ethereal layer was separated and the aqueous phase was extracted with additional ether. Evaporation of the combined extracts gave 17.94 g of solid that was dissolved in ether and passed through a magnesia–silica column using ether as the eluting solvent. The initial 750 ml of eluate was evaporated to furnish 14.3 g (21%) of white crystals, mp 122–126°. This material was of suitable purity for oxidation to the benzoquinone. A sample was recrystallized from ether–hexane to furnish white crystals, mp 139°.

*Anal.* Calcd for $C_7H_4ClF_3O_2$: C, 39.55; H, 1.90; Cl, 16.68, F, 26.82. Found: C, 39.73; H, 2.21; Cl, 16.44; F, 26.61.

**2-Chloro-3-trifluoromethylhydroquinone.**—Hydrogen chloride was introduced into a stirred solution of 2.00 g (11.3 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**5**) in 50 ml of chloroform for 90 min. The solvent was removed, and the residue was recrystallized from hexane to furnish 2.07 g (87%) of crystals, mp 101–109°, of suitable purity for further transformations.

(16) J. B. Conant and L. F. Fieser, *J. Amer. Chem. Soc.*, **46**, 1860 (1924).

(17) A. J. Hollander, *Rec. Trav. Chim. Pays-Bas*, **39**, 481 (1920).

(18) (a) H. H. Hodgeson and D. E. Nicholson, *J. Chem. Soc.*, 645 (1941); (b) *ibid.*, 375 (1942).

(19) A. F. Helin, A. Sveinbjornsson, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **73**, 1189 (1951).

A specimen was recrystallized several times from hexane to furnish white needles, mp 111–114°.

*Anal.* Calcd for $C_7H_4ClF_3O_2$: C, 39.55; H, 1.90; Cl, 16.68; F, 26.82. Found: C, 39.83; H, 1.99; Cl, 16.76; F, 26.32.

**Oxidation of Hydroquinones to Quinones.**—The following preparation of **2-chloro-5-trifluoromethyl-1,4-benzoquinone (12b)** illustrates the general procedure. A mixture of 2.52 g (11.9 mmol) of 2-chloro-5-trifluoromethylhydroquinone, 12.50 g of silver oxide, and 7.50 g of sodium sulfate in 100 ml of ether was stirred at ambient temperature for 17.5 hr. The mixture was filtered, and the residue was washed with ether until the washes were colorless. The combined filtrate and washings were passed through a magnesia–silica gel column using ether as the eluting solvent. The yellow eluate was evaporated, and the residue was recrystallized from ether–hexane to give 1.63 g (65%) of lemon yellow plates: mp 110–111°; $\lambda_{max}$ 5.92, 5.98, 8.75 μ.

*Anal.* Calcd for $C_7H_2ClF_3O_2$: C, 39.93; H, 0.96; Cl, 16.84; F, 27.08. Found: C, 40.02; H, 1.04; Cl, 17.04; F-26.70.

**2-Chloro-3-trifluoromethyl-1,4-benzoquinone (9b)**, formed in 87% yield, was obtained from ether–hexane as yellow crystals: mp 109–110°; $\lambda_{max}$ 5.92, 6.00, 6.10, 8.75 μ.

*Anal.* Calcd for $C_7H_2ClF_3O_2$: C, 39.93; H, 0.96; Cl, 16.84; F, 27.08. Found: C, 39.97; H, 0.92; Cl, 17.09; F, 27.31.

**2-Methoxy-5-trifluoromethyl-1,4-benzoquinone (15)** was prepared from the corresponding hydroquinone[12a] in 90% yield. It was obtained from ether–hexane as yellow crystals: mp 101–102°; $\lambda_{max}$ 5.91, 6.00, 6.12, 6.21, 8.65 μ.

*Anal.* Calcd for $C_8H_5F_3O_3$: C, 46.61; H, 2.45; F, 27.65. Found: C, 46.67; H, 2.60; F, 27.67.

***t*-Butyl 3-aminocrotonate (2b).**—A rapid stream of ammonia gas was introduced into 100 g of *t*-butyl acetoacetate for 6 hr while the mixture was heated on a steam bath. Addition of 100 ml of hexane followed by cooling in a Dry Ice bath gave 72 g (72%) of crystals which partially melted at room temperature. This material was shown by glpc to be homogeneous.

Material prepared in a similar manner was recrystallized several times from hexane to give colorless waxy crystals: mp 37–39°; $\lambda_{max}$ 274 mμ (ε 16,000); 2.94, 3.02, 3.39, 6.05, 6.18, 6.42 μ.

*Anal.* Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.04; H, 9.67; N, 8.64.

**Nenitzescu Condensations.**—The following experiment illustrates the general procedure. A solution of 600 mg (2.86 mmol) of 2-chloro-3-trifluoromethyl-1,4-benzoquinone (**9**) and 368 mg (2.86 mmol) of ethyl 3-aminocrotonate (**2a**) in 25 ml of methanol was heated at reflux temperature for 2.5 hr. The solvent was removed, and the residue crystallized from benzene–heptane to furnish 720 mg (78%) of crystals, mp 133–135°. The characterization of this substance and other indoles prepared in a similar manner is given in Table II.

In those instances wherein the product failed to crystallize or the presence of isomeric indoles was indicated by tlc, the crude reaction mixtures were submitted for partition chromatography on diatomaceous silica.[20]

**Ethyl *trans*-3-Ethylamino-2-(α,α,α-trifluoro-2,5-dihydroxy-*o*-tolyl)crotonate (7).**—A solution of 0.88 g (5.0 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**5**) and 0.65 g (5.0 mmol) of ethyl 3-ethylaminocrotonate (**2c**)[2] in 20 ml of acetone was heated at reflux temperature for 2.5 hr. Removal of the solvent, and trituration of the residue with ether furnished 0.68 g (41%) of pale yellow crystals: mp 122–123°; $\lambda_{max}$ 218, 292 mμ (ε 15,300, 16,300); 3.08, 5.91, 6.21, 6.44, 8.12, 8.58, 8.73, 8.83, 8.99 μ; nmr, 1.2 (overlapping triplets, $J$ = 7.5 cps, $CH_3$), 2.23 (=$CCH_3$), 3.21–4.25 (overlapping multiplets, $CH_2$), 6.15 and 6.90 ppm (doublets, $J$ = 10 cps, aryl protons).[21]

*Anal.* Calcd for $C_{15}H_{18}F_3NO_4$: C, 54.05; H, 5.45; F, 17.10; N, 4.21. Found: C, 53.88; H, 5.38; F, 16.89; N, 4.25.

**Ethyl 1-Ethyl-5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylate (6c).**—A solution of 333 mg (1.0 mmol) of ethyl *trans*-3-ethylamino-2-(α,α,α-trifluoro-2,5-dihydroxy-*o*-tolyl)-crotonate (**7**) and 18 mg (0.1 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**5**) in 10 ml of glacial acetic acid was heated on the steam bath for 1 hr. The solvent was removed, and the residue crystallized from acetone–hexane to give 270 mg (86%) of crystals: mp 189–191°; $\lambda_{max}$ 221, 250, 307 mμ (ε 29,900, 11,200, 9800); 3.00, 6.00, 6.16, 6.31 μ; nmr, 1.21, 1.25 (overlapping triplets, $J$ = 7.5 cps, $CH_2CH_3$), 2.49 (singlet, $CH_3$), 4.16, 4.20 (overlapping quartets, $J$ = 7.5 cps, $CH_2CH_3$), 6.91, 7.56 (doublets, $J$ = 9.0 cps, aryl protons), 9.8 ppm (broad, O*H*).[21]

*Anal.* Calcd for $C_{15}H_{16}F_3NO_3$: F, 18.08; N, 4.45. Found: F, 17.87; N, 4.49.

**Hydrolytic Decarbalkoxylation of the Ethyl 5-Hydroxy-2-methylindole-3-carboxylates.**—The following experiment illustrates the general procedure. A stirred mixture of ethyl-6-chloro-5-hydroxy-2-methyl-7-trifluoromethylindole-3-carboxylate (**10b**) (300 mg, 0.04 mmol) in 20 ml of 20% hydrochloric acid was heated at reflux temperature for 1.5 hr. All solid has dissolved after 30 min. The hot solution was filtered, and the cooled filtrate was rendered alkaline by the addition of a concentrated potassium hydroxide solution. The pH of this solution was rendered acid to litmus paper with hydrochloric acid, and this solution was extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated. The residue was recrystallized from ether–hexane to give 96 mg (56%) of crystals, mp 116–120°. Decolorization of this material was effected by dissolution in methylene chloride and passage of this solution through a magnesia–silica gel column using methylene chloride as the wash solvent. The solid obtained by solvent removal was recrystallized from methylene chloride–hexane to furnish 45 mg of **6-chloro-2-methylindol-5-ol (11b)** as white crystals: mp 119.0–120.5°; $\lambda_{max}$ 273, 288 mμ (ε 8420, 8050); 2.96, 6.33, 6.48 μ.

*Anal.* Calcd for $C_9H_8ClNO$: C, 59.52; H, 4.44; Cl, 19.52; N, 7.72. Found: C, 59.68; H, 4.65; Cl, 19.75; N, 7.50.

Similar treatment of ethyl 6-chloro-5-hydroxy-2-methylindole-3-carboxylate (**3b**) afforded 56% of **11b** as white crystals, mp 116–119°, identical with the above material by the usual criteria.

**2-Methylindol-5-ol (8)** was obtained in 50% by similar treatment of ethyl 5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylate (**6a**) as white crystals, mp 132–134° (lit.[5] mp 134°). This material was identical in all respects with that prepared by similar treatment of ethyl 5-hydroxy-2-methylindole-3-carboxylate.[1,6]

**7-Chloro-2-methylindol-5-ol (14)** was obtained in a similar manner from ethyl 7-chloro-5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylate (**13**) as white crystals (22%): mp 152–154°; $\lambda_{max}$ 277 mμ (ε 8600); 3.00, 6.10, 6.32, 6.70 μ; nmr, 2.38 (singlet, $CH_3$), 6.00 (3-*H*), 6.64 and 6.83 (doublets, 4- and 6-*H*, $J$ = 2.5 cps), 8.34 (broad, O*H*), and 10.0 ppm (N*H*).[22]

*Anal.* Calcd for $C_9H_8ClNO$: C, 59.52; H, 4.44; Cl, 19.52; N, 7.72. Found: C, 59.46; H, 4.67; Cl, 19.72, N, 7.67.

***t*-Butyl 5-Methoxy-2-methyl-4-trifluoromethylindole-3-carboxylate (18).**—A solution of 1.58 g (5.0 mmol) of *t*-butyl 5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylate (**6b**) and 700 mg (5.5 mmol) of dimethyl sulfate in 25 ml of acetone was heated at reflux temperature with 1.5 g of anhydrous $K_2CO_3$ for 2 hr. After removal of the inorganics, the filtrate was evaporated. The residue was dissolved in benzene and this solution was washed with water, dried, evaporated. The residue was crystallized from ether–hexane to furnish 1.2 g (73%) of white crystals, mp 175–179°. A sample for analysis was sublimed at 135° and 0.05 mm to give crystals: mp 188–191°; $\lambda_{max}$ 220, 304 mμ (ε 32,800, 9800); 3.12, 3.36, 6.00, 6.30, 6.70, 6.98, 7.43 μ.

*Anal.* Calcd for $C_{16}H_{18}F_3NO_3$: C, 58.35; H, 5.51; F, 17.31; N, 4.25. Found: C, 58.41; H, 5.59; F, 17.51; N, 4.16.

**2-Methyl-4-trifluoromethylindol-5-ol (19a).**—A solution of 1.5 g of *t*-butyl 5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylate (**6b**) and 130 mg of *p*-toluenesulfonic acid monohydrate in 180 ml of benzene was heated at reflux temperature for 3 hr. The cooled solution was washed with water, dried, and evaporated to give a tan oil. Trituration with warm hexane gave 60 mg of white needles, mp 80–82°. Evaporation of the mother liquor followed by crystallization from hexane gave an additional 500 mg, mp 78–82° (50%). Crystallization of the first crop from hexane gave the analytical specimen: mp 80–82°; $\lambda_{max}$ 224, 305 (ε 23,200, 9400); 2.88; 3.08, 6.12, 6.30, 7.40, 8.46 μ.

*Anal.* Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; F, 26.49; N, 6.51. Found: C, 56.04; H, 3.80; F, 27.05; N, 6.38.

**5-Methoxy-2-methyl-4-trifluoromethylindole (19b).**—A solution of 400 mg of *t*-butyl 5-methoxy-2-methyl-4-trifluoromethylindole-3-carboxylate and 30 mg of *p*-toluenesulfonic acid monohydrate in 30 ml of toluene was heated at reflux temperature for 1 hr. After dilution with benzene, the solution was washed

(20) For a complete description of this technique as developed by C. Pidacks, see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(21) Determined in dimethyl sulfoxide-$d_6$.

(22) Determined in deuteriochloroform–dimethyl sulfoxide-$d_6$.

with water, dried, and evaporated. The resulting solid was recrystallized from ether–hexane to give 183 mg (66%) of white needles, mp 118–121°. A sample for analysis was sublimed at 105° and 0.05 mm to give crystals: mp 118–121°; $\lambda_{max}$ 225, 304 ($\epsilon$ 28,000, 10,000); 2.92 6.15, 6.30, 6.70, 6.96, 7.40 $\mu$.

*Anal.* Calcd for $C_{11}H_{10}F_3NO$: C, 57.63; H, 4.40; F, 24.87; N, 6.11. Found: C, 57.54; H, 4.48; F, 25.13; N, 6.05.

The nmr spectrum of a sample from a similar experiment showed resonances at 2.42 (singlet, 2-C$H_3$), 3.88 (singlet, OC$H_3$), 6.31 (broad, 3-$H$), 6.83, 7.42 (doublets, 6 and 7 H, $J$ = 9.5 cps), 10.3 ppm (broad, N$H$).[22]

**2,4-Dimethyl-5-methoxyindole (20).**—A mixture of 3.5 g of 5-methoxy-2-methyl-4-trifluoromethylindole (**19b**) and 3.5 g of lithium aluminum hydride in 500 ml of tetrahydrofuran was heated at reflux temperature in an inert atmosphere for 3 days. Water was cautiously added, and the reaction mixture was filtered. The filtrate was evaporated and the residue was dissolved in ether, washed with water, dried, and evaporated. The resulting pasty solid was dissolved in dichloromethane and passed through a short column of silica gel. Evaporation gave 2.2 g (82%) of yellow crystals, mp 50–52°. The analytical specimen was prepared by sublimation at 50° and 0.05 mm to give pale yellow crystals: mp 54–55°; $\lambda_{max}$ 274 ($\epsilon$ 8500); 3.00, 3.42, 6.28, 6.66 $\mu$; nmr, 2.26 (singlet, 4-C$H_3$), 2.35 (singlet, 2-C$H_3$), 3.73 (singlet, OC$H_3$), 6.05 (broad, 3-$H$), 6.68, 7.06 (doublets, 6- and 7-$H$, $J$ = 8.0 cps), 10.55 ppm (broad, N$H$).[21]

*Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.78; H, 7.67; N, 8.01.

**Registry No.**—2-Chloro-5-trifluoromethylhydroquinone, 16052-86-1; 2-chloro-3-trifluoromethylhydroquinone, 16052-87-2; **2b**, 16052-66-7; **3a**, 16052-67-8; **3b**, 16052-68-9; **3c**, 16052-44-1; **3d**, 16052-45-2; **4a**, 16052-46-3; **4b**, 16052-47-4; **4d**, 16052-48-5; **6a**, 16052-49-6; **6b**, 16052-50-9; **6c**, 16052-51-0; **7**, 16052-52-1; **9**, 16052-53-2; **10**, 16052-54-3; **11**, 16052-55-4; **12**, 16052-56-5; **13**, 16109-67-4; **14**, 16052-57-6; **15**, 16052-58-7; **16**, 16052-59-8; **17**, 16052-60-1; **18**, 16052-61-2; **19a**, 16052-62-3; **19b**, 16052-63-4; **20**, 16052-64-5.

**Acknowledgment.**—We are indebted to Mr. L. Brancone and his staff for the microanalyses, to Mr. W. Fulmor and his associates for the spectral data, and to Mr. C. Pidacks and his group for the partition chromatography. The large-scale preparation of certain intermediates by Mr. W. Smith with the cooperation of Dr. P. J. Kohlbrenner is gratefully acknowledged.

# Ring Expansions. I. Ring Expansion of the Epimeric *trans*-2-Aminomethyl-2-decalols and *trans*-2-Decalone

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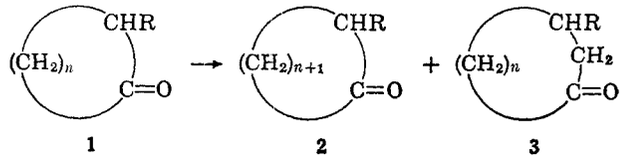
*Received December 26, 1967*

In order to assess the importance of the stereochemistry of the amino alcohols utilized in the Tiffeneau–Demjanov ring expansions of unsymmetrical ketones, the ring expansions of *trans*-2$\alpha$-aminomethyl-2$\beta$-decalol (**10**) and *trans*-2$\beta$-aminomethyl-2$\alpha$-decalol (**11**) have been examined. Ring expansion of amino alcohol **11** gave approximately equal amounts of the two possible ring expanded ketones, *trans*-bicyclo[5.4.0]undecan-3-one (**13**) and *trans*-bicyclo[5.4.0]undecan-4-one (**14**), whereas ring expansion of **10** gave **13** and **14** in the ratio 1:1.6. Ring expansion of *trans*-2-decalone with diazomethane gave a product distribution similar to that obtained from the ring expansion of amino alcohol **10** indicating predominant equatorial attack by diazomethane.

The use of ring expansion reactions for the homologation of cyclic compounds has been an important method for the synthesis of a variety of compounds which could be obtained only with difficulty by other methods. Among the most widely used methods of ring expansion are the reaction of cyclic ketones with diazo compounds[1] and the Tiffeneau–Demjanov[2] rearrangement of amino alcohols derived from the cyclic ketones. For symmetrical ketones both methods are often satisfactory, although in the reaction of cyclic ketones with a diazo compound the initial ring expanded ketones may undergo further reaction to produce undesired higher homologs. The chief disadvantage of the Tiffeneau–Demjanov sequence is the inconvenience of the several additional steps necessary for conversion of the ketone into the required amino alcohol.




1 2 3

When an unsymmetrical ketone (*e.g.*, **1**) is subjected to ring expansion by one of these methods, two possible ring expanded ketones (**2** and **3**) may be formed and it is difficult to predict in advance which will be the major product of the reaction. An examination of the results available in the literature suggests that several factors may be involved in determining the course of the ring expansion of unsymmetrical ketones. Among these factors are (a) the migratory aptitudes of the competing carbon centers, (b) the method of ring expansion, (c) the experimental conditions, (d) conformational and steric effects in the transition state, and (e) the effect of remote substituents.

On the basis of factor a, it might be anticipated on electronic grounds that the more substituted carbon should migrate preferentially by analogy with other reactions involving migrations to electron-deficient centers[3–6] and this type of behavior has been observed in some cases. For example, the diazomethane ring expansion of 2,2-dimethylcyclohexanone is reported to give only 3,3-dimethylcycloheptanone.[7] In contrast,

(1) C. D. Gutsche, *Org. Reactions*, **8**, 364 (1954).
(2) P. A. S. Smith and D. R. Baer, *ibid.*, **11**, 157 (1960).
(3) M. Stiles and R. P. Mayer, *J. Amer. Chem. Soc.*, **81**, 1497 (1959).
(4) Rearrangements in the semipinacolic deamination reaction are much less sensitive to substituent effects than other rearrangements such as the pinacol rearrangement. For example, in the pinacol rearrangement, the migration ratio *p*-anisyl/phenyl is 500[5] whereas in the semipinacolic deamination of 2-amino-1,1-diarylethanols the ratio is only 1.56.[6]
(5) W. E. Bachman and J. W. Ferguson, *J. Amer. Chem. Soc.*, **56**, 2081 (1934).
(6) D. Y. Curtin and M. C. Crew, *ibid.*, **76**, 3719 (1954).
(7) R. A. Barnes and W. J. Houlihan, *J. Org. Chem.*, **26**, 1609 (1961).