Observations on the Mechanism of the Nenitzescu Indole Synthesis and Its Utilization for the Preparation of Carbazoles[1]

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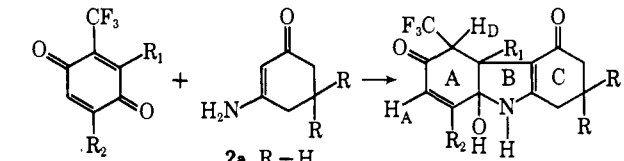
Abstract: The reaction of 2-trifluoromethyl-1,4-benzoquinone (**1a**) with 3-amino-2-cyclohexen-1-one (**2a**) and its 5,5-dimethyl derivative (**2b**) is solvent, temperature, and time dependent. In acetic acid at ambient temperature **1a** reacts with **2a** and **2b** to give 4a,7,8,9a-tetrahydro-9a-hydroxy-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (**3a**) and its 7,7-dimethyl derivative **3b**, respectively. 2-Chloro-5-trifluoromethyl-1,4-benzoquinone (**1c**) and enamine **2b** furnish 1-chloro 4a,7,8,9a-tetrahydro-9a-hydroxy-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (**3d**) under these reaction conditions. In refluxing ethanol, quinone **1a** and enamine **2a** afford tetrahydrocarbazoledione **3a**, rather than the 5-hydroxyindole type derivative which is usually formed in this medium. If boiling acetic acid is the reaction medium, quinone **1a** and enamines **2a** and **2b** give 5,6,7,8-tetrahydro-3-hydroxy-5-oxo-4-carbazolecarboxylic acid (**5a**) and the 7,7-dimethyl derivative **5b**, respectively. Acids **5a** and **5b** also result from carbinolamines **3a** and **3b**, respectively, on treatment with a catalytic amount of quinone **1a** in refluxing acetic acid for 16 hr. 2,3-Dihydro-6-hydroxy-2,2-dimethyl-5-trifluoromethyl-4(1*H*)-carbazolone (**6**) is an apparent intermediate in this transformation of **3b** into **5b**, inasmuch as it is the main product when the reaction is interrupted after 4 hr and can be converted into acid **5b** on further treatment with boiling acetic acid. Enamine **2b** reacts with 2-acetyl-1,4-benzoquinone (**8a**) to give 3,4-dihydro-7,10-dihydroxy-3,3,6-trimethyl-1(2*H*)-phenanthridinone (**9**). Treatment of **2b** with 2-carbomethoxy-1,4-benzoquinone (**8b**) affords the methyl ester **10** of acid **5b** and 3,4-dihydro-7,10-dihydroxy-3,3-dimethyl-1,6(2*H*)-phenanthridinedione (**11**). The reaction of enamines **2** with 2-methoxy-1,4-benzoquinone (**12**) furnishes the 2,3-dihydro-6-hydroxy-7-methoxy-4(1*H*)-carbazolones (**13**). The suggested intermediacy of carbinolamines **3** in the formation of tetrahydrocarbazolecarboxylic acids **5** is investigated, and the relevance of the results with respect to a mechanism proposed for the Nenitzescu condensation is discussed.

The utility of the reaction of 1,4-benzoquinones with alkyl 3-aminocrotonates and enamines derived from linear β-diketones for the preparation of alkyl 5-hydroxyindole-3-carboxylates[2] and 3-acyl-5-hydroxyindoles,[3] respectively, is well documented. These investigations suggest that the reaction of quinones with enamines derived from cyclohexane-1,3-diones might constitute a useful synthesis of carbazole derivatives. New procedures for the preparation of carbazoles are of interest since this class of compounds continues to be detected as plant constituents[4] as they often are degradation products of more complex alkaloids.[5] In this paper we describe the preparation of representative carbazoles by reaction of certain substituted 1,4-benzoquinones with 3-amino-2-cyclohexen-1-ones. Moreover, our results afford further insight regarding the mechanism[2b,6] of the Nenitzescu synthesis.

1,4-Benzoquinone and toluquinone react with 3-amino-2-cyclohexen-1-one (**2a**) and 3-amino-5,5-dimethyl-2-cyclohexan-1-one (**2b**) in acetic acid or ethanol to give a multiplicity of products (tlc evidence), precluding preparative value.[7] However, reaction of enamines **2** with those quinones possessing substituent activation is often of synthetic utility, the structure of the products being dependent on the quinone substituent, reaction solvent, time, and (or) temperature. Thus, 2-trifluoromethyl-1,4-benzoquinone (**1a**) reacts exothermally with enamines **2a** and **2b** in acetic acid to give the carbinolamines **3a** and **3b**, respectively, after 15–45 min (see Scheme I). The former product also results

Scheme I



1a, $R_1 = R_2 = H$
b, $R_1 = R_2 = D$
c, $R_1 = H$; $R_2 = Cl$

2a, R = H
b, R = Me

3a, R = H; $R_1 = H_C$; $R_2 = H_B$
b, R = Me; $R_1 = H_C$; $R_2 = H_B$
c, R = Me; $R_1 = R_2 = D$
d, R = Me; $R_1 = H_C$; $R_2 = Cl$

in 55% yield by reaction of **1a** and **2a** in refluxing ethanol; this last observation contrasts markedly to the many reported 5-hydroxyindole preparations carried out in this medium. Microanalyses and spectral data provided proof that the normal Nenitzescu condensation had not occurred. Thus, microanalyses indicated that the products contained all atoms of the reactants, precluding elimination of the elements of water as required by a normal Nenitzescu condensation.

(1) For a preliminary report, see R. Littell, G. O. Morton, and G. R. Allen, Jr., *Chem. Commun.*, 1144 (1969).

(2) (a) C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, 11, 37 (1929); *Chem. Abstr.*, 24, 110 (1930); (b) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 2536 (1966).

(3) A. N. Grinev, V. I. Shvedov, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **26**, 1449 (1956); *Chem. Abstr.*, **50**, 14710i (1956).

(4) (a) D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Tetrahedron*, **21**, 681 (1965); (b) B. S. Joshi, V. N. Kamat, A. K. Saksena, and T. R. Govindachari, *Tetrahedron Lett.*, 4019 (1967).

(5) R. E. Moore and H. Rapoport, *J. Org. Chem.*, **32**, 3335 (1967).

(6) D. Raileanu and C. D. Nenitzescu, *Rev. Roumaine Chim.*, 10, 339 (1965).

(7) Benzoquinone[1a,8] and toluquinone[1b,9] also afford several products with ethyl 3-aminocrotonate. However, favorable solubility properties make possible the isolation of ethyl 5-hydroxy-2-methylindole-3-carboxylate and its 6- and 7-methyl derivatives from these reactions.

(8) S. A. Monti, *J. Org. Chem.*, **31**, 2669 (1966).

(9) G. R. Allen, Jr., L. J. Binovi, and M. J. Weiss, *J. Med. Chem.*, 10, 7 (1967).

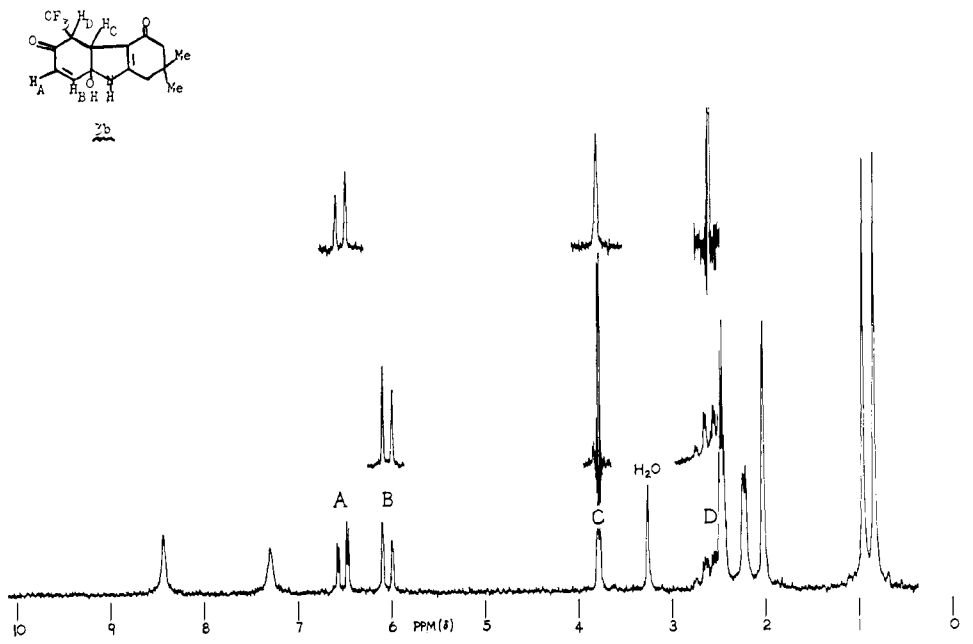
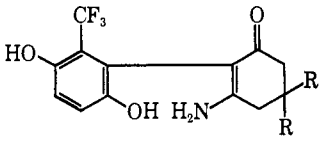


Figure 1. 100-MHz nmr spectrum of 4a,7,8,9a-tetrahydro-9a-hydroxy-7,7-dimethyl-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (**3b**).

Moreover, the ultraviolet spectra resemble the spectra of enamines **2**[10] and are in complete discord for compounds having a 3-acylindole chromophore.[11]

Two structures, carbinolamine **3** and hydroquinone **4**, satisfy these criteria. Hydroquinones such as **4** have been observed as side products in Nenitzescu condensations,[2b,6,8] and their ultraviolet spectra also resemble those of the enamine reactant. In the present instance alternative structures **3** and **4** are the most reasonable in view of steric and electronic considerations, for each results from carbon–carbon bond formation at the most electropositive carbon of quinone **1a**.[12] Additionally, carbinolamines **3** are the products of nitrogen–carbon condensation at the less hindered carbonyl group.[13]



4a, R = H
b, R = Me

The 100-MHz nmr spectrum of carbinolamine **3b** and appropriate decoupling experiments distinguished between the alternative structures. In this connection we note that the 7,7-*gem*-dimethyl grouping in **3b** facilitated the interpretation by removing an apparent 7-proton envelope present in the spectrum of **3a**. Amino (δ 8.44), hydroxy (δ 7.30), and nonequivalent methylene (δ 2.23, 2.02) and methyl (δ 0.96, 0.84) proton resonances are apparent in the spectrum of **3b** (see Figure 1). The lower field methylene protons are nonequivalent, their chemical shifts differing by δ 0.03. Four single-proton resonances at δ 6.51, 6.06, 3.79, and 2.60 are uniquely compatible with the carbinolamine structure **3b**. The last resonance is an apparent 16-line pattern, one-fourth of which is hidden by the resonance of dimethyl sulfoxide solvent; the remaining resonances are doubled doublets. Irradiation of proton C removes long-range coupling with proton B to give a sharp doublet (J_{AB} = 10 Hz) and causes collapse of the proton D multiplet into a sharp apparent eight-line pattern (J_{D-CF_3} = 9.2 Hz, J_{AD} = 2.0 Hz). The ^{19}F spectrum confirms the coupling of proton D with fluorine, for the single resonance at Φ +61.9 is a doublet (J_{CF_3-D} = 9.2 Hz). Finally, irradiation of proton D causes coalescence of the proton A resonance into a sharp doublet (J_{AB} = 10 Hz) and collapse of the proton C resonance into an ill-defined doublet (J_{BC} = 1.0 Hz). Comparison of these spectra suggests coupling of protons C and D with J_{CD} = 3.0 Hz.

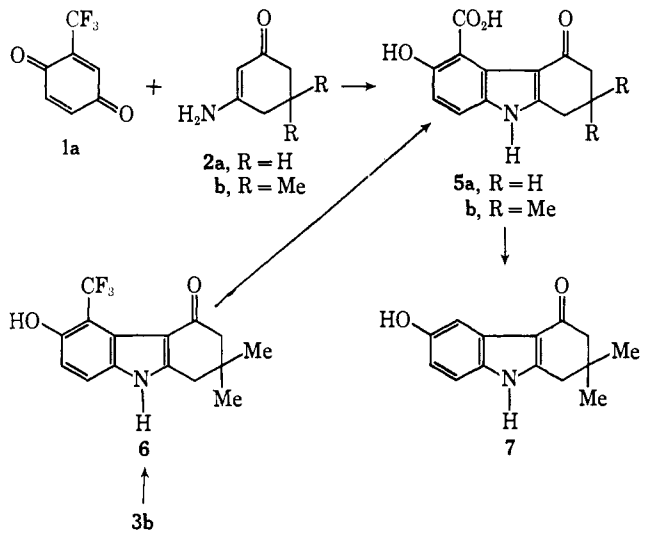
The magnitude of J_{CD}, J_{D-CF_3}, and J_{AD} coupling constants is confirmed by the spectra of carbinolamines **3c** and **3d**, which were prepared by reaction of enamine **2b** with 2-trifluoromethyl-1,4-benzoquinone-3,5-*d* (**1b**) and 2-chloro-5-trifluoromethyl-1,4-benzoquinone (**1c**), respectively. The spectra of **3c** and **3d** clearly show J_{D-CF_3} = 9.2 Hz and J_{AD} = 2.0 Hz. Moreover, the spectrum of **3d** defines J_{CD} = 3.0 Hz.

Compound **3b** is a weak acid, insoluble in water and dilute bicarbonate solution, but soluble in dilute caustic. Acidification of the conjugate base affords **3b**, suggesting a *cis* junction for rings A/B. Similar treatment of the corresponding *trans*-fused system should result in elimination of the elements of water with concomitant aromatization of ring A. Moreover, inspection of Dreiding models suggests that the *cis*-fused system would be favored.

Treatment of quinone **1a** in boiling acetic acid with enamines **2a** (4 hr) and **2b** (16 hr) gives the tetrahydrocarbazolecarboxylic acids **5a** and **5b**, respectively (see Scheme II). The *ortho* orientation of the bz-ring substituents in these products is dictated by their nmr spectra, which show two aryl proton resonances with J = 8.5 Hz. Comparison of the nmr spectrum of **5b** with that of its decarboxylation product **7** requires that

(10) Uv max for **2b** is 286 mμ (ε 27,800).
(11) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).
(12) R. Littell and G. R. Allen, Jr., *ibid.*, **33**, 2064 (1968).
(13) See ref 2b for a more complete discussion of steric and electronic effects in the reaction of quinones with enamines.

Scheme II

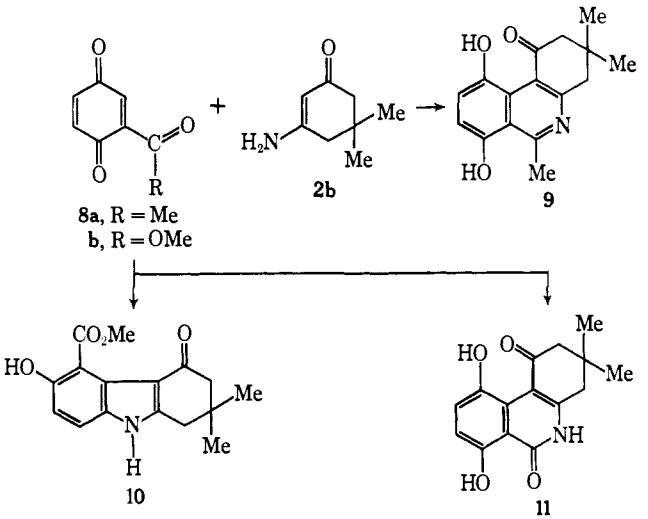


the carboxyl group in the former substance be located at C-4. Thus, the spectrum of **7** exhibits an additional aryl proton resonance at δ 7.25, possessing a typical *meta* coupling constant (J = 2.5 Hz). The low-field chemical shift of this resonance indicates that the proton introduced by decarboxylation occupies a *peri* relationship to the deshielding carbonyl group.[2b,14]

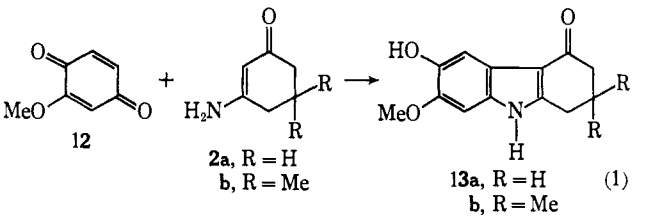
The carboxylic acids **5a** and **5b** may also be prepared by treatment of carbinolamines **3a** and **3b**, respectively, with 0.1 mol equiv of quinone **1a** in refluxing acetic acid for 16 hr. These transformations indicate a common nucleus for carbinolamines **3** and acids **5** and suggest the intermediacy of a trifluoromethylcarbazole, *e.g.*, **6**, in the conversion of **3** into **4**.[15] Interruption of the reaction of carbinolamine **3b** with quinone **1a** at 4 hr supports this suggestion, for trifluoromethylcarbazole **6** (15%) and acid **5a** (9%) are the isolated products. The structure of the former product follows from its ultraviolet spectrum (λ_{max} 217, 256, 268, 300 mμ), which requires a 3-acylindole chromophore,[11] and its nmr spectrum, in which two single aryl proton resonances with J = 8.5 Hz confirm *ortho* orientation for the bz substituents. The conversion of trifluoromethylcarbazole **6** into acid **5b** by boiling acetic acid confirms the structural array and supports the intermediacy of **6** in the conversion of carbinolamine **3b** into acid **5b**.

Those quinones in which the substituent activates the *ortho* position by electron-withdrawing conjugative effects, *e.g.*, 2-acetyl- and 2-carbomethoxy-1,4-benzoquinone, react with enamines **2a** and **2b** in a manner analogous to their behavior with alkyl 3-aminocrotonates.[17] Thus, 2-acetyl-1,4-benzoquinone (**8a**) reacts with enamine **2b** to furnish phenanthridinone **9** in 17% yield (see Scheme III). In the instance of carbomethoxy quinone (**8b**) reaction with enamine **2b** gives 30% of the methyl 5-ketotetrahydrocarbazole-4-carboxylate **10** and 60% of phenanthridinedione **11**. The former product is identical with that prepared by Fischer esterification of acid **5b**. One distinction exists in the reaction of quinone **8b** with ethyl 3-aminocrotonate and enamine **2b**. The initially formed Michael adduct assumes *trans* (ring–amine) geometry with the former enamine, precluding completion of indole or isocarbostyril formation. The Nenitzescu synthesis is completed only after equilibration of the initial adduct under oxidizing conditions.[17] In contrast, the initial adduct from enamine **2b** must assume *cis* geometry, the consequence of which is the observed ring closure.

Scheme III



Finally, enamines **2a** and **2b** react with 2-methoxy-1,4-benzoquinone (**12**), in which the substituent is strongly electron donating, to give the anticipated 7-methoxycarbazole derivatives **13a** and **13b**, respectively (eq 1).



(1)

Mechanistic Considerations. Two mechanisms, differing in the order of the required nitrogen–carbon and carbon–carbon condensations, have been proposed for the Nenitzescu indole synthesis. The mechanism involving initial carbon–carbon condensation is more consistent with enamine chemistry,[18] and recent studies confirmed its validity for the Nenitzescu reaction.[2b,6] However, the alternate mechanism[19] is compatible with certain aspects of quinone chemistry,[20] and the earlier studies failed to exclude its intervention. Experiments with carbinolamines **3a** and **3b** now provide compelling evidence against the mechanism in which initial nitrogen–carbon condensation occurs.

Although the genesis of carbinolamines **3** is not clear, they formally represent products of initial nitrogen–carbon condensation (Scheme IV).[21] The conversion

(14) W. A. Remers, *J. Amer. Chem. Soc.*, 86, 4608 (1964).

(15) The acid and alkaline hydrolytic conversion of certain hydroxybenzotrifluorides into hydroxybenzoic acids has been reported.[16]

(16) W. B. Whalley, *J. Chem. Soc.*, 3016 (1949).

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

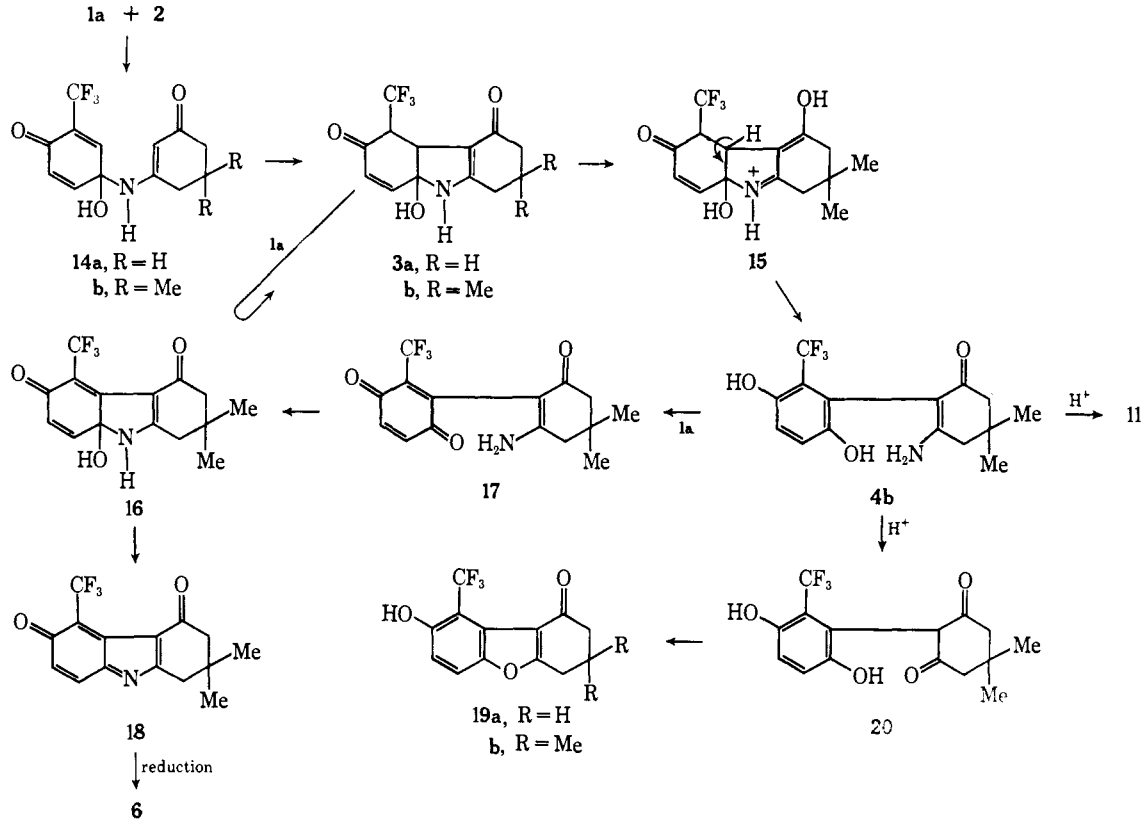
(18) (a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 85, 207 (1963); (b) J. Szmuszkovicz, *Advan. Org. Chem.*, 4, 1 (1963); (c) A. G. Cook, "Enamines: Synthesis, Structure, and Reactions," Marcel Dekker, New York, N. Y., 1969.

(19) E. A. Steck, R. P. Brundage, and L. F. Fletcher, *J. Org. Chem.*, 24, 1750 (1959).

(20) Z. E. Jolles in "Chemistry of Carbon Compounds," E. H. Rodd, Ed., Vol. III, Elsevier Publishing Co., New York, N. Y., 1956, p 714.

(21) Compounds **3** may represent the kinetic products of initial carbon–carbon condensation, for the rate of aromatization (K_1) of the

Scheme IV



of **3a** and **3b** into tetrahydrocarbazolecarboxylic acids **5a** and **5b** by treatment with quinone **1a** in boiling acetic acid suggests their intermediacy in the Nenitzescu synthesis. Three pathways for these transformations are apparent: (1) acid-catalyzed dehydration to give the 5-trifluoromethyl precursor, *e.g.*, **6**; (2) dehydrogenation of **3** by quinone **1a** to furnish dienone **16**, which functions as an intermediate for trifluoromethylcarbazolone **6** by the previously demonstrated mechanism; and (3) fragmentation of carbinolamines **3** into quinone **1a** and enamine **2b**, recombination of which furnishes the acids **5**. However, appropriate experiments eliminated each of these routes from consideration.

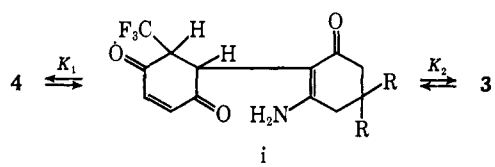
Thus, treatment of carbinolamine **3b** with acetic acid (under conditions of time and temperature required for its conversion into acid **5b** with added quinone **1a**) gives dibenzofuranone **19** and phenanthridinedione **11** as the only products (Scheme IV). The latter product is identical in all respects with that prepared from enamine **2b** and carbomethoxyquinone **8b** (see above). Moreover, mineral acid treatment of carbinolamine **3a** initiates a process which is more complex than simple elimination, since dibenzofuranone **19a** results.

The direct formation of carbinolamine **3a** from quinone **1a** and enamine **2a** in refluxing ethanol, a medium often employed for the Nenitzescu procedure, suggests that the conversion of **3a** into acid **5a** is not initiated by quinone **1a** dehydrogenation. However, if the formation of carbinolamine **3a** proceeds at a rate greater than its dehydrogenation, quinone **1a** would not be available for the latter function in these circumstances. Nevertheless, the recovery of carbinolamine **3b**, following its treatment with 1 equiv of quinone **1a** in boiling methanol, precludes its conversion into acid **5a** by initial dehydrogenation.

Finally, deuterium-labeling experiments argue convincingly against the fragmentation–recombination mechanism. Treatment of carbinolamine **3b** with 0.18 mol equiv of 2-trifluoromethyl-1,4-benzoquinone-3,5-*d* (**1b**) in boiling acetic acid gives acid **5b**, the nmr spectrum of which reveals no incorporation of deuterium at C-1. Reaction of carbinolamine-1,4a-*d* **3c** with quinone **2a** for 16 hr in this medium furnished even more decisive results. The isolated 1-deuterio analog of acid **5b** possessed no ^1H at C-1 as detectable by nmr. Moreover, if this reaction is interrupted after 4 hr, the nmr spectrum of the isolated trifluoromethylcarbazolone **6**-3,3,8-*d* shows the absence of **6** and **6**-3,3-*d* in the product. The fragmentation–recombination mechanism requires the presence of the ^1H species in the products of the last two experiments, for in this circumstance quinones **1a** and **1b** would be available for reaction with enamine **2b**.

These results indicate that carbinolamines **3** are not intermediates, *per se*, in the Nenitzescu synthesis. In fact, the above evidence *precludes that mechanism involving initial nitrogen–carbon condensation and indicates that such products are transformed into indoles only after conversion into compounds resulting from initial carbon–carbon condensation.* Thus, the dominant reaction of carbinolamines **3** in acid is protonation of

initially formed adduct **i** into hydroquinone **4** could be slower than the nitrogen–carbon condensation (K_2) leading to carbinolamines **3**. However, the available evidence precludes the formation of **3** from hydroquinone **4** by a Bucherer-type reaction.[2b]



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the enamine system to furnish hydroquinone **4** *via* **15**.[22] In accord with this concept, treatment of carbinolamine **3b** with boiling acetic acid for 5 min gives 85% of hydroquinone **4b**. In the presence of oxidant, *e.g.*, quinone **1a**, **4b** is converted into quinone **17** and thence into carbazole derivative **6** (or **5b**) by the previously demonstrated mechanism (**16** → **18** → **6**).[2b,6] Thus, hydroquinone **4b** gives 22% of acid **5b** when treated with quinone **1a** (0.18 equiv) in boiling acetic acid for 16 hr. In the absence of oxidant, hydrolysis of the enamine system and the trifluoromethyl group of **4b**, respectively, affords dibenzofuranone **19** and phenanthridone **11**.

Experimental Section

General. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The infrared (ir) spectra were determined in pressed potassium bromide disks with a Perkin-Elmer spectrophotometer, and the ultraviolet (uv) spectra were determined in methanol solution using a Cary recording spectrophotometer. Nmr spectra were determined in the indicated solvent on a Varian A-60 spectrometer; in the instance of compound **3b** the spectrum was determined and the decoupling experiments were performed with a Varian HR-100 spectrometer. Chemical shifts are given in parts per million downfield from an internal tetramethylsilane standard. The fluorine nmr spectrum was determined on a Varian HR-60 at 56.4 Mcps using $CFCl_3$ as an external standard. Mass spectra were determined with an AEI MS-9 spectrometer. All evaporations were carried out at reduced pressure.

4-Nitro-3-trifluoromethylphenol-2,6-*d*. This substance was prepared by a modification of Ingold's procedure.[23] A mixture of 4.14 g (0.02 mol) of 4-nitro-3-trifluoromethylphenol and 0.69 g (0.005 mol) of potassium carbonate in 10 ml of deuterium oxide (99.5% min) was heated in a sealed Pyrex tube at 155–158° for 120 hr. The cooled reaction was acidified with dilute hydrochloric acid and extracted five times with benzene. The dried extracts were evaporated to give 4.06 g (97%) of pale yellow crystals: mp 76–78°; nmr ($CDCl_3$) δ 7.97 (s, 1, C-*H*), 6.40 (s, 1, O*H*). Integration of the nmr trace indicated this material to be approximately 95% pure.

4-Amino-3-trifluoromethylphenol-2,6-*d*. A mixture of 3.94 g (18.9 mmol) of 4-nitro-3-trifluoromethylphenol-2,6-*d* and 0.3 g of 10% palladium-on-charcoal in 50 ml of ethanol was shaken under deuterium in a Parr apparatus for 75 min. The filtered mixture was evaporated, the residue was dissolved in methanol, and this solvent was removed. The methanol addition and removal were repeated twice to give 3.53 g of nearly white crystals; a 100-mg sample was recrystallized from benzene–heptane to give 82 mg of white blades: mp 158–159°; nmr ($CDCl_3$–DMSO-d_6) δ 8.50 (1, O*H*), 6.67 (s, 1, >C—*H*), 3.97 (s, 2, N*H*$_2$).

2-Trifluoromethyl-1,4-benzoquinone-3,5-*d* (1b). This substance was prepared from 3.43 g (19.2 mmol) of 4-amino-3-trifluoromethylphenol-2,6-*d* by oxidation with 5.96 g (20 mmol) of sodium dichromate dihydrate as described previously:[12] yield, 1.74 g (52%); mp 52–54°; nmr ($CDCl_3$) δ 6.97 (s, >C—*H*).

4a,7,8,9a-Tetrahydro-9a-hydroxy-4-trifluoromethylcarbazole-3,5-(4*H*,6*H*)-dione (3a). A. A solution of 600 mg (3.4 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**1a**) and 380 mg (3.4 mmol) of 3-amino-2-cyclohexen-1-one (**2a**)[24] in 5 ml of ethanol was heated at reflux temperature for 1 hr. Benzene (5 ml) was added, and the cooled mixture was filtered to give 500 mg (55%) of **6a** as a tan powder, mp 215° dec. A sample recrystallized from methanol and then from ethanol was obtained as white crystals: mp 215° dec; uv max 218, 278, 295 mμ (ϵ 14,300, 13,400, 11,700); ir max 3.15, 6.05, 6.22 μ; nmr (DMSO-d_6) δ 8.44 (broad s, 1, N*H*), 7.30 (s, 1, O*H*), 6.06 (dd, 1, $J_{1,2}$ = 10 Hz, $J_{2,4}$ = 2.0 Hz, 2-*H*), 6.00 (dd, 1, $J_{1,2}$ = 10 Hz, $J_{1,4a}$ = 1.0 Hz, 1-*H*), 3.85 (dd, 1, $J_{4,4a}$ = 3.0 Hz, $J_{1,4a}$ = 1.0 Hz, 4a-*H*), 2.64–1.50 (envelope).

Anal. Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; F, 19.84; N, 4.88. Found: C, 54.06; H, 4.28; F, 19.08; N, 4.92.

B. A solution of 1.90 g (1.08 mmol) of quinone **1a** and 1.11 g (1.0 mmol) of 3-amino-2-cyclohexene-1-one (**2a**) in 10 ml of acetic acid was allowed to stand at ambient temperature for 15 min. The resulting mixture was cooled and filtered to give 640 mg (22%) of white crystals, mp 215° dec.

4a,7,8,9a-Tetrahydro-9a-hydroxy-7,7-dimethyl-4-trifluoromethylcarbazole-3,5-(4*H*,6*H*)-dione (3b). A solution of 6.00 g (34 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**1a**) and 1.40 g (10 mmol) of 3-amino-5,5-dimethyl-2-cyclohexen-1-one (**2b**)[24] in 10 ml of acetic acid was allowed to warm by the exotherm (45°). Crystals appeared, and after 0.5 hr the mixture was cooled and filtered. The residue was washed with ether to give 1.10 g (35%) of white crystals, mp 235–240° dec. A sample was recrystallized from methanol to give crystals: mp 237–240° dec; uv max 220, 280, 295 mμ (ϵ 14,200, 13,000, 11,400); ir max 3.15, 6.00, 6.23 μ; the nmr spectrum is given in the Discussion; mass spectrum (70 eV), M^+ 315.

Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.13; H, 5.16; F, 18.08; N, 4.44. Found: C, 57.38; H, 5.17; F, 18.25; N, 4.51.

4a,7,8,9a-Tetrahydro-9a-hydroxy-7,7-dimethyl-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione-1,4a-*d* (3c). In the manner described for the preparation of **3b**, 633 mg (3.55 mmol) of 2-trifluoromethyl-1,4-benzoquinone-3,5-*d* (**1b**) and 450 mg (3.20 mmol) of 3-amino-5,5-dimethyl-2-cyclohexen-1-one (**2b**) in 3 ml of acetic acid gave 430 mg (43%) of **3c** as crystals; this material was slurried in acetone and filtered to give 390 mg of crystals: mp 232–234° dec; nmr (DMSO-d_6) δ 8.44 (broad s, 1, N*H*), 7.33 (broad, 1, O*H*), 6.55 (d, 1, $J_{2,4}$ = 2.0 Hz, 2-*H*), 2.63 (m, 1, $J_{2,4}$ = 2.0 Hz, J_{4,CF_3} = 9.5 Hz, 4-*H*), 2.27 (s, 2, 8-C*H*$_2$), 2.07 (s, 2, 6-C*H*$_2$), 1.00 (s, 3, 7-C*H*$_3$), 0.89 (s, 3, 7-C*H*$_3$); mass spectrum (70 eV), M^+ 317.

1-Chloro-4a,7,8,9a-tetrahydro-9a-hydroxy-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (3d). A solution of 421 mg (2.0 mmol) of 2-chloro-5-trifluoromethyl-1,4-benzoquinone (**1c**)[12] and 278 mg (2.0 mmol) of **2a** was allowed to stand at room temperature for 30 min and then chilled in ice. The separated solid was collected by filtration, washed with benzene, and dried to give 247 mg (35%) of crystals, mp 243–245° dec. Recrystallization from dilute methanol furnished 182 mg of nearly white crystals: mp 250–251° dec; uv max 238, 282, 292 (sh), 355 (ϵ 14,200, 13,600, 12,300, 2100); ir max 3.01, 3.14, 5.90, 6.18, 6.35 μ; nmr (DMSO-d_6) δ 8.65 (s, 1, N*H*), 7.60 (s, 1, O*H*), 6.81 (d, 1, $J_{2,4}$ = 2.0 Hz, 2-*H*), 4.04 (d, 1, $J_{4,4a}$ = 3.0 Hz, 4a-*H*), 2.82 (m, 1, $J_{2,4}$ = 2.0 Hz, $J_{4,4a}$ = 3.0 Hz, J_{4,CF_3} = 9.5 Hz, 4-*H*), 2.31 2.10 (s, 2, C*H*$_2$), 1.01 (s, 3, 7-C*H*$_3$), 0.87 (s, 3, 7-C*H*$_3$).

Anal. Calcd for $C_{15}H_{13}ClF_3NO_3$: C, 51.51; H, 4.32; Cl, 10.14; F, 16.30; N, 4.00. Found: C, 51.76; H, 4.43; Cl, 10.56; F, 16.44; N, 4.14.

5,6,7,8-Tetrahydro-3-hydroxy-5-oxo-4-carbazolecarboxylic Acid (5a). A. A mixture of 2.80 g (9.75 mmol) of 4a,7,8,9a-tetrahydro-9a-hydroxy-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (**3a**) and 300 mg (1.7 mmol) of **1a** in 20 ml of acetic acid was heated at reflux temperature for 4 hr. Filtration of the cooled mixture gave 550 mg (23%) of crystals, mp 260° dec. A sample recrystallized from propyl alcohol had mp 324–326° dec; uv max 213, 278 mμ (ϵ 19,800, 20,200); ir max 2.90, 3.10, 6.20, 6.50 μ; nmr (DMSO-d_6) δ 7.32 (d, 1, $J_{1,2}$ = 8.5 Hz, 1-*H*), 6.80 (d, 1, $J_{1,2}$ = 8.5 Hz, 2-*H*), 2.95 (m, 2, 8-C*H*$_2$), *ca.* 2.40 (obscured by DMSO resonance, C*H*$_2$), *ca.* 2.12 (m, 2, C*H*$_2$).

Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.47; H, 4.50; N, 5.73.

B. Acid **5a**, mp 324–326° dec, was obtained in 24% yield by heating a mixture of 1.16 g (6.6 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**1a**) and 666 mg (6.0 mmol) of 3-amino-2-cyclohexen-1-one (**2a**) in 10 ml of acetic acid at reflux temperature for 4 hr.

5,6,7,8-Tetrahydro-3-hydroxy-7,7-dimethyl-5-oxo-4-carbazolecarboxylic Acid (5b). A. A solution of 2.20 g (12.5 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**1a**) and 1.40 g (10 mmol) of 3-amino-5,5-dimethyl-2-cyclohexen-1-one (**2b**) in 13 ml of acetic acid was heated at reflux temperature for approximately 16 hr. Filtration of the cooled reaction mixture gave 670 mg (25%) of **5b**, mp 262–264° dec. This material was recrystallized from dimethylformamide–propyl alcohol to give crystals: mp 266–268° dec; uv max 278 mμ (ϵ 20,000); ir 3.18, 3.40, 6.28, 6.50 μ; nmr (DMSO-d_6) δ 7.35 (d, 1, $J_{1,2}$ = 8.5 Hz, 1-*H*), 6.80 (d, 1, $J_{1,2}$ = 8.5 Hz, 2-*H*), 2.83 (s, 2, 8-C*H*$_2$), 2.38 (s, 2, 6-C*H*$_2$), 1.07 (s, 6, C(C*H*$_3$)$_2$); mass spectrum (70 eV), M^+ 273.

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.92; H, 5.48; N, 4.88.

B. Acid **5b**, mp 260–262° dec, was obtained in 28% yield by heating a mixture of 500 mg of 4a,7,8,9a-tetrahydro-9a-hydroxy-

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7,7-dimethyl-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (**3b**) and 50 mg of **1a** in 10 ml of acetic acid at reflux temperature for 16 hr.

C. Treatment of 180 mg of 2,3-dihydro-6-hydroxy-2,2-dimethyl-5-trifluoromethyl-4(1*H*)-carbazolone (**6**) with 2 ml of boiling acetic acid for 20 hr gave acid **5b**, mp 268–270° dec, in 30% yield.

D. A solution of 300 mg (0.95 mmol) of 3-amino-2-(α,α,α-trifluoro-3,6-dihydroxy-*o*-tolyl)-5,5-dimethyl-2-cyclohexen-1-one (**4b**) and 30 mg (0.17 mmol) of **1a** in 3 ml of acetic acid was heated at reflux temperature for 20 hr. The cooled mixture was filtered to give 65 mg (22%) of **5b**, mp 275–278°.

2,3-Dihydro-6-hydroxy-2,2-dimethyl-4-(1*H*)-carbazolone (7). A solution of 3.50 g (12.7 mmol) of 5,6,7,8-tetrahydro-3-hydroxy-7,7-dimethyl-5-keto-4-carbazolecarboxylic acid (**5b**) in 80 ml of concentrated HCl and 50 ml of water was heated at reflux temperature for 4 hr. Neutralization of the acid solution with KOH solution gave 1.70 g (58%) of tan crystals, mp 286° dec. The analytical sample was obtained as white crystals: mp 287° dec, by sublimation at 200° under reduced pressure; uv max 215, 253, 277, 300 mμ (ε 19,700, 26,000, 14,300; 11,000); ir max 3.15, 3.40, 6.15 μ; nmr (DMSO-d_6) 11.50 (broad, 1, N*H*), 8.84 (s, 1, O*H*), 7.35 (d, 1, $J_{5,7}$ = 2.5 Hz, 5-*H*), 7.15 (d, 1, $J_{7,8}$ = 8.5 Hz, 8-*H*), 6.63 (dd, 1, $J_{5,7}$ = 2.5 Hz, $J_{7,8}$ = 8.5 Hz, 7-*H*), 2.78 (s, 2, 1-CH_2), 2.28 (s, 2, 3-CH_2), 1.07 (s, 6, C(CH_3)$_2$).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.15; H, 6.80; N, 6.08.

2,3-Dihydro-6-hydroxy-2,2-dimethyl-5-trifluoromethyl-4(1*H*)-carbazolone (6). A mixture of 2.00 g (6.35 mmol) of 4a,7,8,9a-tetrahydro-9a-hydroxy-7,7-dimethyl-4-trifluoromethylcarbazole-3,5-(4*H*,6*H*)-dione (**3b**) and 200 mg (1.13 mmol) of 2-trifluoromethyl-1,4-benzoquinone (**1a**) in 20 ml of acetic acid was heated at reflux temperature for 4 hr, cooled, and filtered to give 500 mg of impure (tlc) amorphous, yellow powder. This material was crystallized from methanol–acetone to give 150 mg (9%) of **5,6,7,8-tetrahydro-3-hydroxy-7,7-dimethyl-5-oxo-4-carbazolecarboxylic acid (5b)**, mp 267–269°.

The crystallization filtrate was evaporated and the residue was submitted to partition chromatography[25] on diatomaceous silica using the solvent system heptane–ethyl acetate–methanol–water (60:40:15:6). The fraction with peak hold-back volume 8.4 (V_m/V_s = 2.5) was evaporated and the residue was recrystallized from acetone to give 275 mg (15%) of **6** as white crystals, mp 255–265° dec. The analytical sample was obtained by two additional recrystallizations from acetone: mp 265–267° dec; uv max 217, 256, 268 (sh), 300 (sh) (ε 17,400, 12,200, 6500); ir max 3.00, 3.36, 6.10, 6.27 μ; nmr (DMSO-d_6) 9.70 (broad s, 1, N*H*), 7.42 (d, 1, $J_{7,8}$ = 8.5 Hz, 8-*H*), 6.86 (d, 1, $J_{7,8}$ = 8.5 Hz, 7-*H*), 2.85 (s, 2, 1-CH_2), 2.35 (s, 2, 3-CH_2), 1.05 (s, 6, C(CH_3)$_2$); mass spectrum (70 eV), M^+ 297.

Anal. Calcd for $C_{15}H_{14}F_3NO_2$: C, 60.60; H, 4.75; F, 19.18; N, 4.71. Found: C, 60.72; H, 4.68; F, 19.19; N, 5.05.

3,4-Dihydro-7,10-dihydroxy-3,3,6-trimethyl-1(2*H*)-phenanthridinone (9). A solution of 2.00 g (13.3 mmol) of 2-acetyl-1,4-benzoquinone (**8a**)[26] and 1.68 g (12 mmol) of 3-amino-5,5-dimethyl-2-cyclohexen-1-one (**2b**) in 20 ml of ethanol was heated at reflux temperature for 5 hr. The solvent was evaporated, and the residue was dissolved in chloroform, washed with water, dried, and evaporated. The residue was chromatographed on silica gel, and the fraction eluted with ether–methylene chloride (1:9) was evaporated. Crystallization of the residue from methylene chloride–hexane gave 540 mg (17%) of crystals, mp 208–212° dec. The analytical sample was obtained as glistening maroon plates: mp 218–220° dec; uv max 275, 350, 385 mμ (ε 17,500, 3400, 3800); ir max 2.95, 3.42, 6.10, 6.30 μ; nmr (DMSO-d_6) δ 10.2 (broad s, 1, O*H*), 9.93 (broad s, 1, O*H*), 7.08, 7.06 (equiv s, 2, 8-*H*, 9-*H*), 3.06 (overlapping s, 5, 6-CH_3, 4-CH_2), 2.75 (s, 2, 2-CH_2), 1.09 (s, 6, 2-CH_3).

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.84; H, 6.30; N, 5.14.

Reaction of 2-Carbomethoxy-1,4-benzoquinone (8b) with 3-Amino-5,5-dimethyl-2-cyclohexen-1-one (2b). A solution of 2.17 g (13 mmol) of **8b**[27] and 1.68 g (12 mmol) of **2b** in 20 ml of ethanol was heated at reflux temperature for 4 hr. The reaction was cooled and filtered to give 1.58 g (48%) of 3,4-dihydro-7,10-dihydroxy-3,3-dimethyl-1,6(2*H*)-phenanthridinedione (**11**) as an orange powder, mp 306–308° dec. Crystallization from methanol gave orange needles: mp 310–312° dec; uv max 220, 280, 355 mμ (ε 20,200, 11,200, 8200); ir max 3.40, 6.05, 6.15, 6.25 μ: nmr (DMSO-d_6) δ 12.4 (s, 1, O*H*), 11.0 (s, 1, N*H*), 7.10 (d, 1, $J_{8,9}$ = 10 Hz, 8- or 9-*H*), 6.85 (d, 1, $J_{8,9}$ = 10 Hz, 8- or 9-*H*), 2.85 (s, 2, 4-CH_2), 2.62 (s, 2, 2-CH_2), 1.08 (s, 6, 3-C(CH_3)$_2$).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.63; H, 5.42; N, 5.18.

The filtrate was evaporated, and the residue was subjected to partition chromatography on diatomaceous silica using heptane–ethyl acetate–methanol–water (55:45:15:6). The fraction eluted at peak hold-back volume 0.8 (V_m/V_s = 3.0) gave an additional 400 mg (60% total) of **11**, mp 305–307° dec, after removal of the solvent.

The fraction eluted at peak hold-back volume 5.0 was evaporated to give 1.00 g (30%) of methyl 5,6,7,8-tetrahydro-3-hydroxy-7,7-dimethyl-5-keto-4-carbazolecarboxylate (**10**) as a tan powder, mp 168–172°. This material was identical in all respects with that obtained in 95% yield by Fischer (MeOH–HCl) esterification of 5,6,7,8-tetrahydro-3-hydroxy-7,7-dimethyl-5-keto-4-carbazolecarboxylic acid (**5b**). The latter sample was recrystallized from acetone–hexane to give white crystals: mp 171–174°; uv max 216, 257, 274, 300 (sh) mμ (ε 22,000, 16,000, 17,200, 10,000); ir max 3.10, 3.40, 5.85, 6.15 μ; nmr (DMSO-d_6) δ 11.7 (broad s, 1, O*H*), 9.17 (s, 1, N*H*), 7.25 (d, 1, $J_{1,2}$ = 9.0 Hz, 1-*H*), 6.79 (d, 1, $J_{1,2}$ = 9.0 Hz, 2-*H*), 3.81 (s, 3, OCH_3), 2.80 (s, 2, 8-CH_2), 2.28 (s, 2, 6-CH_2), 1.06 (s, 6 C(CH_3)$_2$).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.11; H, 6.30; N, 5.13.

2,3-Dihydro-6-hydroxy-7-methoxy-4(1*H*)-carbazolone (13a). A solution of 10.0 g (72 mmol) of 2-methoxy-1,4-benzoquinone (**12**)[28] and 7.00 g (63 mmol) of 3-amino-2-cyclohexen-1-one (**2a**) in 80 ml of ethanol was heated at reflux temperature for 3 hr; the cooled mixture was filtered and the solid was washed with water and then with methanol to give 6.50 g (45%) of gray powder, mp 285–290°. The analytical sample was obtained as a white powder: mp 293–295°, by recrystallization from methanol and sublimation at 180°; uv max 218, 252, 285, 300 mμ (ε 21,400, 13,700, 18,800, 10,000); ir max 3.16, 3.40, 6.20 μ.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.27; H, 5.59; N, 5.97.

2,3-Dihydro-6-hydroxy-7-methoxy-2,2-dimethyl-4(1*H*)-carbazolone (13b). A solution of 1.10 g (8.0 mmol) of 2-methoxy-1,4-benzoquinone (**12**) and 1.00 g (7.3 mmol) of 3-amino-5,5-dimethyl-2-cyclohexen-1-one (**2b**) in 10 ml of ethanol was heated at reflux temperature for 5 hr. Filtration of the cooled solution gave 750 mg (40%) of tan crystals, mp 290° dec. Several recrystallizations of this material from methanol gave white crystals, mp 299–301° dec; uv max 215, 250, 285, 310 (sh) mμ (ε 28,800, 13,700, 14,600, 11,000); ir max 2.84, 3.15, 3.40, 6.18, 6.28 μ; nmr (DMSO-d_6) δ 11.5 (broad s, 1, N*H*), 8.47 (s, 1, O*H*), 7.35 (s, 1, 5-*H*), 6.88 (s, 1, 8-*H*), 3.78 (s, 3, OCH$_3$), 2.77 (s, 2, 1-CH_2), 2.27 (s, 2, 3-CH_2), 1.07 (s, 6, C(CH_3)$_2$).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.75; H, 6.85; N, 5.49.

Treatment of 4a,7,8,9a-Tetrahydro-9a-hydroxy-7,7-dimethyl-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (3b) with Acetic Acid. A mixture of 300 mg of **3b** and 3 ml of acetic acid was heated at reflux temperature for 18 hr; solution occurred after approximately 3 hr. Addition of methanol and water to the cooled solution gave 110 mg (37%) of orange powder, mp 265° dec. Crystallization from methanol gave **3,4-dihydro-7,10-dihydroxy-3,3-dimethyl-1,6(2*H*)-phenanthridinedione (11)** as orange needles, mp 295–300° dec. This material was identical by the usual criteria with that prepared above.

The filtrate was evaporated, and the residue was chromatographed on 20 g of silica gel. The material eluted by ether–chloroform was recrystallized from acetone–hexane to give 65 mg (23%) of **3,4-dihydro-8-hydroxy-3,3-dimethyl-9-trifluoromethyl-1(2*H*)-dibenzofuranone (19b)** as colorless crystals: mp 194–197°; uv max 208, 238, 255 (sh), 300 mμ (ε 26,400, 14,500, 9500, 7200); ir max 3.15, 6.00, 6.15, 6.27, 6.40 μ; nmr (DMSO-d_6), δ 10.3 (broad, 1, O*H*), 7.69 (d, 1, $J_{6,7}$ = 9.0 Hz, 6-*H*), 7.04 (d, 1, $J_{6,7}$ = 9.0 Hz, 7-*H*), 2.98 (s, 2, 4-CH_2), 2.48 (s, 2, 2-CH_3), 1.10 (s, 6, C(CH_3)$_2$).

Anal. Calcd for $C_{15}H_{13}F_3O_3$: C, 60.42; H, 4.36; F, 19.12. Found: C, 60.40; H, 4.35; F, 19.58.

(25) For a complete description of this technique as developed by Mr. 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).

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3,4-Dihydro-8-hydroxy-9-trifluoromethyl-1(2*H*)-dibenzofuranone (19a). A solution of 700 mg of 4a,7,8,9a-tetrahydro-9a-hydroxy-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (**3a**) in 15 ml of 20% HCl was heated at reflux temperature for 2 hr, cooled, and diluted with water. Filtration gave 370 mg (55%) of pale yellow powder, mp 240–250° dec. Crystallization from methanol gave the analytical specimen as a white powder: mp 272–274° dec; uv max 210, 238, 255 (sh), 300 mμ (ε 27,500, 15,500, 10,500, 7000); ir max 3.24, 6.04, 6.15, 6.27, 6.40 μ; nmr (DMSO-d_6) δ 10.3 (broad, O*H*), 7.72 (d, 1, $J_{6,7}$ = 10 Hz, 6-*H*), 7.02 (d, 1, $J_{6,7}$ = 10 Hz, 7-*H*), 3.05 (t, 2, J = 7 Hz, 3-CH_2), 2.75–1.83 (envelope).

Anal. Calcd for $C_{13}H_9F_3O_3$: C, 57.78; H, 3.36; F, 21.10. Found: C, 58.02; H, 3.31; F, 21.04,

5,6,7,8-Tetrahydro-3-hydroxy-7,7-dimethyl-5-keto-4-carbazolecarboxylic acid-1-*d*. Treatment of 250 g of 4a,7,8,9a-tetrahydro-9a-hydroxy-7,7-dimethyl-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione-1,4a-*d* (**3c**) with 25 mg of **1a** in 2.5 ml of acetic acid as described in method B for the preparation of **5b** gave 70 mg (32%) of 5,6,7,8-tetrahydro-3-hydroxy-7,7-dimethyl-5-keto-4-carbazolecarboxylic acid-1-*d*, mp 270–272° dec. The nmr spectrum of this material showed a sharp singlet at δ 6.80 (2-*H*).

2,3-Dihydro-6-hydroxy-2,2-dimethyl-5-trifluoromethyl-4(1*H*)-carbazolone-3,3,8-*d*. Treatment of 4a,7,8,9a-tetrahydro-9a-hydroxy-7,7-dimethyl-4-(trifluoromethyl)-carbazole-3,5-(4*H*,6*H*)-dione-1,4a-*d* (**3c**) with 60 mg of **1a** in 6 ml of acetic acid-d_4 at reflux temperature for 4 hr gave white crystals, mp 260–265° dec. The nmr spectrum of this material showed a sharp singlet at δ 6.85 (7-*H*).

3-Amino-2-(α,α,α-trifluoro-3,6-dihydroxy-*o*-tolyl)-5,5-dimethyl-2-cyclohexen-1-one (4b). A suspension of 900 mg (2.86 mmol) of 4a,7,8,9a-tetrahydro-9a-hydroxy-7,7-dimethyl-4-trifluoromethylcarbazole-3,5(4*H*,6*H*)-dione (**3b**) in 9 ml of acetic acid was heated rapidly to reflux temperature. Although solution did not occur, a visual change in the character of the solid was observed. After 3 min the mixture was filtered to give 760 mg (84%) of white crystals, mp 264–266° dec.

Material from a similar experiment was recrystallized from ethanol–acetone to give crystals: mp 285° dec; uv max 230, 290 mμ (ε 6300, 25,000); ir max 2.85, 2.95, 3.00, 3.40, 6.05, 6.52 μ; nmr (DMSO-d_6) δ 9.22 (s, 1, O*H*), 8.03 (s, 1, O*H*), 6.78 (s, 2, aryl *H*), 5.72 (broad s, 2, NH_2), 2.27 (s, 2, 4-CH_2), 2.05 (s, 2, 6-CH_2), 1.05, 1.02 (nonequivalent s, 6, C(CH_3)$_2$).

Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.13; H, 5.16; F, 18.08; N, 4.44. Found: C, 57.36; H, 5.25; F, 18.42; N, 4.33.

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Semisynthetic Polypeptides. Transformation of Native Porcine β-Melanotropin into the Lysine-10 Analog of the Human Hormone[1]

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Abstract: To determine the utility of preparing peptide analogs by a semisynthetic approach, the lysine-10 analog of human β-melanotropin, a docosapeptide, was synthesized by treating native porcine β-MSH with a suitably blocked azide of alanylglutamyllysyllysine. In addition to the desired straight-chain semisynthetic peptide, a branched-chain product was obtained, the result of acylation of an N^{ϵ} site of porcine β-melanotropin.

The combination of native and synthetic peptides provides a method alternate to total synthesis for the preparation of polypeptide analogs. Such a semisynthetic approach may be particularly useful for the convenient introduction of limited amino acid substitutions in enzymes or other large molecules in order to examine the molecular basis of specificity of action or the nature of forces stabilizing tertiary structure. Semisynthesis, widely employed in the preparation of analogs of many natural products, has only rarely been applied in peptide chemistry. Among reports on the use of native substrates for the synthesis or study of well characterized peptide analogs are those recorded by Dixon, *et al.*,[4] on transamination of amino-terminal residues, and on transformation of corticotropin[5] into [Gly[1]]-corticotropin,[6] by Katsoyannis, *et al.*,[7] on the combination of native and synthetic chains of insulin, and by Hofmann, *et al.*,[8] on interactions of synthetic S-peptide analogs with native S-protein of ribonuclease. Milne and Carpenter[9] employed *t*-butyloxycarbonylamino acids for acylation of insulin in the formation of di- and triaminoacylinsulins. Only the latter study, however, was concerned with the formation of new peptide bonds and the consequent necessity for

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