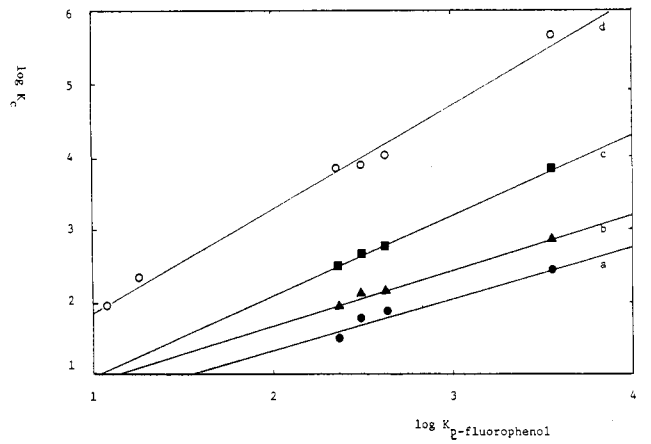


**Figure 1.** Log–log plot of equilibrium constants for hydrogen bonding of four imides to various bases vs values for *p*-fluorophenol hydrogen bonding to the same bases. (a) 2-ethyl-2-methylsuccinimide (●), (b) 2-chloro-3-methylmaleimide (▲), (c) 2,3-dichloro-2-methylsuccinimide (■), (d) tetrafluorosuccinimide (○).

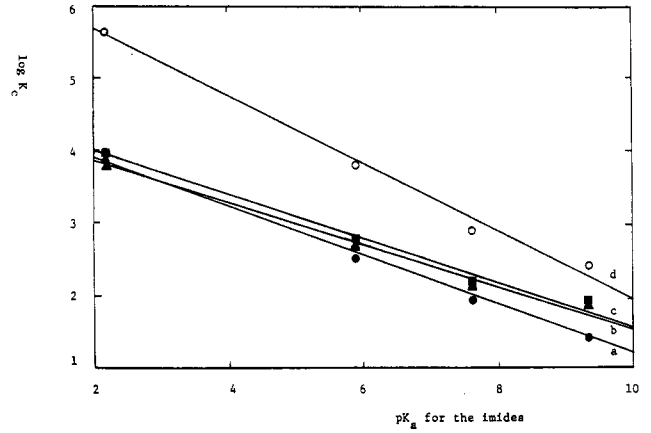


**Figure 2.** Plot of logarithms of equilibrium constants for hydrogen bonding of various imides to four bases vs $pK_a$ values for the imides. (a) *N*-methyl-2-pyrrolidone (●), (b) dimethyl sulfoxide (▲), (c) tetramethylene sulfoxide (■), (d) hexaphosphoramide (○).

has been observed previously with OH acids.[2]

Figure 2 is a log–log plot of the equilibrium constants in carbon tetrachloride for the four stronger bases vs the $pK_a$ values of the imides in water, both at 25 °C. Since we were not able to determine the $pK_a$ of tetrafluorosuccinimide, we estimated it by assuming that the tetrafluoro substituents would have the same effect on the $pK_a$ of succinimide (9.35 at an unstated temperature[17]) that they do on the $pK_a$ of pyrrolidinium ions (11.305[18]). The $pK_a$ of 3,3,4,4-tetrafluoropyrrolidinium ions is 4.05;[19] hence the $pK_a$ of tetrafluorosuccinimide should be about 2.1. The relatively good straight lines are analogous to those reported previously for phenols.[2]

Such straight lines as those in Figures 1 and 2 are presumably just approximations to parts of long gradual curves; extrapolation of the straight line leads to the improbable conclusions that 2-ethyl-2-methylsuccinimide would be a stronger hydrogen bonder than tetrafluorosuccinimide toward a very weak base and that *N*-methyl-2-pyrrolidone would be stronger than hexamethylphosphoramide toward a very weak acid. The absolute values of the slopes of the lines for *N*-methyl-2-pyrrolidone (0.34), dimethyl sulfoxide (0.29), tetramethylene sulfoxide (0.31), and hexamethylphosphoramide (0.46) show an imperfect tendancy to increase with increasing hydrogen-bonding basicity.

The eight lines in Figures 1 and 2 were described by 16 parameters, eight slopes and eight intercepts. We can also use the method of Miller[20] and apply eq 1, which contains

$$\log K_{b\text{-}im} = apK_{HB} + bpK_a + cpK_{HB}pK_a + d \quad (1)$$

only four parameters. In this equation $K_{b\text{-}im}$ is the equilibrium constant for complexing of an imide with an oxygen base, $pK_{HB}$ is the logarithm of the equilibrium constant for hydrogen bonding of *p*-fluorophenol with the same base, and $pK_a$ is the value for the imide. Least-squares treatment of the 18 $K$ values in Table II gave values of $a$, 1.61 (0.10); $b$, −0.10 (0.02); $c$, −0.08 (0.05); and $d$, 0.62 (0.25). The standard deviation of the calculated from the observed values of log $K_{b\text{-}im}$ was 0.15, which is near 0.14, the average standard deviation of the points from the lines in Figure 2.

**Registry No.** $(Me)_2S{=}O$, 67-68-5; $HO_2C(CF_2)_2CO_2H{\cdot}NH_3$, 112296-54-5; $HO_2C(CF_2)_2CONH_2$, 425-08-1; $HO_2CCH_2C(Me)(Et)CO_2H$, 631-31-2; $Br(CH_2)_4Me$, 110-53-2; *p*-$FC_6H_4OH$, 371-41-5; tetrafluorosuccinimide, 377-33-3; 2,3-dichloro-2-methylsuccinimide, 69636-49-3; 2-chloro-3-methylmaleimide, 69636-50-6; 2-ethyl-2-methylsuccinimide, 77-67-8; *N*-methylpyrrolidone, 872-50-4; tetramethylene sulfoxide, 1600-44-8; hexamethylphosphoramide, 680-31-9; 1-pentyluracil, 13350-87-3; tetrafluorosuccinic anhydride, 699-30-9; citraconimide, 1072-87-3; uracil, 66-22-8.

**Supplementary Material Available:** Sample data on a specific run are listed in Table III and plotted in Figure 3 (2 pages). Ordering information is given on any current masthead page.

(17) Kornfeld, E. C.; Jones, R. G.; Parke, T. V. *J. Am. Chem. Soc.* **1949**, *71*, 150–159.
(18) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1972; compound 5370.
(19) Roberts, R. D.; Spencer, T. A. *Tetrahedron Lett.* **1978**, 2557–2558.
(20) Miller, S. I. *J. Am. Soc.* **1959**, *81*, 101–106.

## Characterization of New Mesomeric Betaines Arising from Methylation of Imidazo[2,1-*c*][1,2,4]triazin-4(1*H*)-one, Pyrazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one, and 1,2,4-Triazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one[1]

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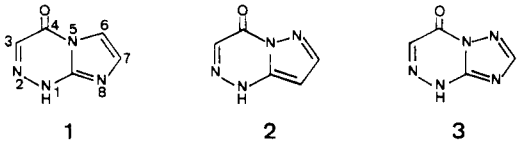
We report here the structure elucidation of the methylation products of imidazo[2,1-*c*][1,2,4]triazin-4(1*H*)-one (**1**) pyrazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one (**2**), and 1,2,4-triazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one (**3**), which forces us to correct a tentative proposal[2] regarding one of the methyl derivatives of **3**. The ylide-like or betaine-like structure of some of them is independently confirmed by NOE experiments and by $^1H$, $^{13}C$, and $^{15}N$ NMR spectra of selectively $^{15}N$-labeled products.



1 2 3

(1) Presented in part at the XIX Reunión Bienal de la Real Sociedad Española de Química (Santander, September 1982). For a precedent paper, within our Diazo-, Azo-, and Azidoazoles series, see ref 5b.
(2) Tennant, G.; Vevers, R. J. S. *J. Chem. Soc. Perkin Trans. 1* **1976**, 421.

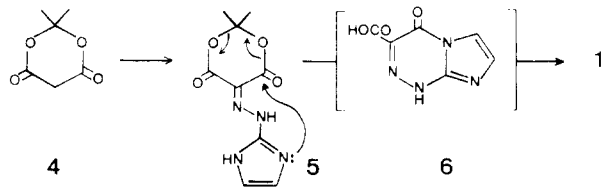
0022-3263/88/1953-0887$01.50/0 

Table I. NMR Spectral Data of Methyl Derivatives of 1–3 in $Me_2SO$-$d_6$

| | 1a | 1b | 1e | 2a | 2c | 2e | 3a | 3b | 3c | 3e |
|---|---|---|---|---|---|---|---|---|---|---|
| δ(H-3) | 7.56 | 8.00 | 8.06 | 7.57 | 8.02 | 7.95 | 7.85 | 8.27 | 8.20 | 8.50 |
| δ(H-6) | 7.76 | 7.70[a] | 7.93 | | | | | | | |
| δ(H-7) | 7.40 | 7.70[a] | 7.79 | 8.05 | 8.32 | 8.17 | 8.41 | 8.99 | 9.00 | 8.54 |
| δ(H-8) | | | | 6.53 | 6.67 | 6.75 | | | | |
| δ($CH_3$) | 3.97 | 3.78 | 4.28 | 3.94 | 4.27 | 4.23 | 4.00 | 3.74 | 4.31 | 4.28 |
| $J_{6,7}$ | 1.8 | [a] | 1.3 | | | | | | | |
| $J_{7,8}$ | | | | 2.2 | 3.5 | 2.2 | | | | |
| δ(C-3) | 126.6 | 133.9 | 118.3 | 127.4 | 134.8 | 119.5 | 132.2 | 139.0 | 139.1[b] | 126.9 |
| δ(C-4) | 150.6 | 148.6 | 152.0 | 148.8 | 151.5 | 150.9 | 149.6 | 147.8 | 150.1 | 150.8 |
| δ(C-6) | 109.1 | 105.4 | 108.5 | | | | | | | |
| δ(C-7) | 131.0 | 123.1 | 136.2 | 144.4 | 140.5 | 145.5 | 153.0 | 144.8 | 151.5 | 155.7 |
| δ(C-8) | | | | 89.2 | 94.9 | 96.7 | | | | |
| δ(C-8a) | 142.8 | 145.8 | 149.6 | 143.5 | 147.9 | 149.3 | 151.5 | 148.6 | 154.5 | 157.2 |
| δ($CH_3$) | 40.9 | 32.0 | 51.2 | 42.9 | 39.8 | 51.1 | 41.4 | 30.7 | 38.8 | 51.6 |

[a] In $D_2O$ these protons are not equivalent: $^1H$ NMR ($D_2O$) δ 3.62 (s, Me), 7.35 (d, $J$ = 2.2, H-7), 7.45 (d, $J$ = 2.2, H-6), 7.85 (s, H-3). [b] This $^{13}C$ NMR spectrum was obtained in MeOH-$d_4$.

Scheme I




Coupling of diazo azoles with active-methylene compounds such as acetylacetone and diethyl malonate constitutes a short and general route to azolo-1,2,4-triazine derivatives.[2-4] An alternative direct way to this N-bridged system related to aza/deazapurines is based on the reaction of diazo azoles with electron-rich alkenes and alkynes.[5] Compound **2** had been prepared from ethyl cyanoacetate and 3-diazo-3*H*-pyrazole[4a] (henceforward 3-diazopyrazole) and compound **3** from diethyl malonate and 3-diazo-3*H*-1,2,4-triazole[2] (henceforward diazo-*s*-triazole), the tautomers shown (**1–3**) being the predominant ones.[6] In the present work **1–3** have been prepared from Meldrum's acid (isopropylidene malonate, **4**)[7] and 2-diazo-2*H*-imidazole (henceforward, 2-diazoimidazole),[8] 3-diazopyrazole, and diazo-*s*-triazole, respectively, in very good overall yields; the coupling between each diazo azole and **4** occurred instantaneously and the cyclization and decarboxylation could be carried in one pot, as shown in Scheme I for compound **1**.[9,10]

Methylation of **3** *under basic conditions*[11] had been reported to give two monomethylated products. Structure **3a** was rigorously established to be the major one, while either structure **3b** or **3c** was tentatively assigned to the minor one.[2] Two other possible structures are the *O*-methyl derivative (**3d**) and the 2-methyl derivative (**3e**).

We have found that when **1** was treated with MeI and KOH in MeOH, two monomethylated products are also obtained. *The major one, the less polar isomer*, showed (i) a C=O bond at 1700 $cm^{-1}$, (ii) a $^1H$ NMR spectrum in $Me_2SO$-$d_6$ (see Table I) that agreed perfectly with those of **1**, **3a**, and 1-methyl-1,2,4-triazolo[3,4-*c*][1,2,4]triazin-4-(1*H*)-one (an isomer of **3a** of well-established structure),[6] and (iii) a $^{13}C$ NMR spectrum (see Table I) which also agreed perfectly with that of **1**; all these data pointed out that structure **1a** was the more reasonable candidate for the major methylated product. *The minor one, the more polar isomer*, showed a medium/strong band at 1680 $cm^{-1}$ and its methyl hydrogens and carbon resonated at δ 4.28 and δ 51.2, respectively, i.e., at lower fields than the corresponding methyl signals of **1a**.

When **2** was methylated under the same conditions, two products were obtained as well. Furthermore, the methylation of **3** in basic medium was repeated, two products being obtained whose melting points and IR, UV, and $^1H$ NMR spectra agree with those reported by Tennant and Vevers.[2] The less polar isomers obtained from **1**, **2**, and **3** were closely related (chromatographically and spectroscopically), so that structures **1a–3a**, respectively, should be attributed to them. The more polar methylation products also showed very similar properties, suggesting the same structural type in each case. *O*-Methyl structures **1d–3d** were ruled out by the presence of IR bands at 1680–1690 $cm^{-1}$ and nonidentity of the more polar products from **1** and **2** with the *O*-methyl isomers **1d** and **2d**, pre-

(3) For a recent review on the chemistry of diazo azoles, see: Tisler, M.; Stanovnik, B. *Khim. Geterotsikl. Soedin.* **1980**, *16*, 579.

(4) (a) Partridge, M. W.; Stevens, M. F. G. *J. Chem. Soc. C* **1966**, 1127. (b) Gray, E. J.; Stevens, M. F. G.; Tennant, G.; Vevers, R. J. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1496 and references therein.

(5) (a) Padwa, A.; Kumagai, T.; Woolhouse, A. D. *J. Org. Chem.* **1983**, *48*, 2330 and references therein. (b) Farràs, J.; Vilarrasa, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1127.

(6) (a) Daunis, J.; Follet, M. *Bull. Soc. Chim. Fr.* **1976**, 1178. (b) Daunis, J.; Follet, M.; Marzin, C. *Org. Magn. Reson.* **1980**, *13*, 330.

(7) (a) Mc Nab, H. *Chem. Soc. Rev.* **1978**, *7*, 345. (b) Mc Nab, H. *J. Org. Chem.* **1981**, *46*, 2809. (c) Jacobs, R. T.; Wright, A. D.; Smith, F. X. *Ibid.* **1982**, *47*, 3769. Also see references therein.

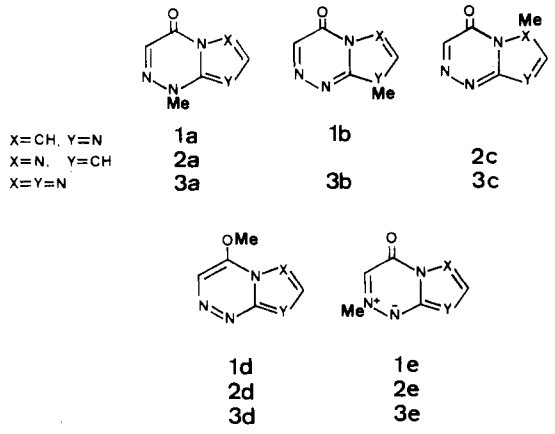
(8) (a) Vilarrasa, J.; Granados, R. *J. Heterocycl. Chem.* **1974**, *11*, 867. (b) Castillón, S.; Meléndez, E.; Vilarrasa, J. *Ibid.* **1982**, *19*, 61. (c) Since the diazonium salts of azoles are relatively strong acids (e.g., for the imidazole-2-diazonium/2-diazoimidazole equilibrium the $pK_a$ value is 2.6 ± 0.1: see, Vilarrasa, J.; Meléndez, E.; Elguero, J. *Tetrahedron Lett.* **1974**, 1609), the diazo compounds are thought to be the species actually involved in most couplings.

(9) In refluxing AcOH, the yellow color of the solution fades after ca. 30 min; **6** can be almost quantitatively isolated at that moment if desired. In the pyrazole case, the intermediate 1,4-dihydro-4-oxopyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylic acid (**7**), isomer of **6**, was obtained when the cyclization was carried out in AcOH; on the other hand, heating of the coupling product in refluxing pyridine afforded directly **2**.

(10) In the case of **1**, the use of **4** is advantageous since 2-diazoimidazole and ethyl cyanoacetate give the desired coupling product at neutral pH but its direct cyclization in hydrochloric acid[4a] affords bad yields of **1**, and since no azo-coupling product is obtained from 2-diazoimidazole and diethyl malonate either under the conditions of Tennant and Vevers[2] or in NaEtO/EtOH to ensure a sufficient concentration of the anion of the active-methylene compound in the medium. The low electrophilicity of 2-diazoimidazole and its unstability under basic conditions[8] explain these last unsuccessful results.

(11) As the $pK_a$ of **3** is 4.9 (Egorova, L. G.; Petrov, A. Yu.; Rusinov, V. L. *Khim. Geterotsikl. Soedin.* **1984**, *20*, 697), the anion of **3** must be the reactive species.

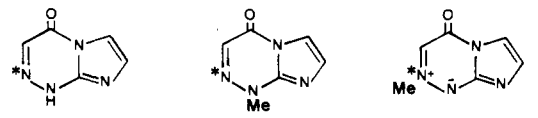
(12) That the δH and δC values are larger than those of **1a** may be due to the fact that N-2 of **1e** is a quaternary nitrogen atom, whereas the $\nu_{CO}$ value for **1e** (lower than usual) is explained by the delocalization of the negative charge. For a recent, comprehensive review on heterocyclic mesomeric betaines, see: Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239.




pared by alternate syntheses.[5b,13] Moreover, the 8-methyl isomer **1b** and 6-methyl isomer **2c** were prepared by independent syntheses and appeared to be different from the methylation product of **1** and **2**.

The betaines **1e–3e** thus remain for the structures of the more polar methylation products. *To corroborate the betaine structures* two sets of experiments were carried out. In the simplest one, homonuclear gated-decoupling experiments on the thought **1–3e** in degassed $Me_2SO$-$d_6$ allowed us to measure nuclear Overhauser enhancements for H-3 of ca. 20% on irradiating the methyl signal, as clearly seen in the NOE difference spectra; viceversa, selective irradiation of H-3 produced enhancements of ca. 5% on the methyl protons. Therefore, the methyl groups and protons H-3 must be very close, as they are found in **1e**, **2e**, and **3e**.[14]

In another set of experiments, we took advantage of a selective $^{15}N$ labeling. Thus, 2-aminoimidazolium sulfate was diazotized with labeled $NaNO_2$ (36% of $^{15}N$ or N*), and the diazo azole was coupled with **4** to give partially labeled **5** (i.e., **5** + **5***), which was cyclized to **1** + **1*** (ca. 65:35) in the usual way. Methylation of **1** + **1*** as above yielded two chromatographically different products—assumed to be **1a** + **1a*** and **1e** + **1e***—which were separated. The $^1H$, $^{13}C$, and $^{15}N$ NMR spectra of **1a** + **1a*** and **1e** + **1e*** are shown in Figure 1 (supplementary material).




What characterizes **1a*** is the $^2J_{H3-N2}$ value of 14.3 Hz, the very small $^1J_{C3-N2}$ value (1.3 Hz), and its $\delta$(N-2) value of −22.3 (i.e., 22.3 ppm to higher field than $H^{15}NO_3$). By contrast, for the second methylation product $^2J_{H3-N2}$ amounts only 2.4 Hz, the $^{13}C$–$^{15}N$ coupling constants are clearly seen ($^1J_{C3-N2}$ = 11.7 Hz and $^1J_{Me-N2}$ = 11.0 Hz, which confirm that the methyl group is linked to the labeled nitrogen as in structure **1e***), and N-2 appears at $\delta$ −129.1. All these values agree with those reported for either pyridine-like nitrogens or pyridinium salts.[15]

Methylation of the *neutral molecules* (**1–3**), without adding a base, using either dimethyl sulfate in refluxing acetonitrile, an excess of dimethyl sulfate without solvent, or cold methyl fluorosulfonate as the solvent, gave more complex mixtures, including unreacted starting material and sometimes dimethylated products. In the case of **1**, the best overall yields of monomethyl derivatives (40% of **1e**, 12% of **1a**, and ca. 4% of **1b**) were obtained with methyl fluorosulfonate, but also with dimethyl sulfate the percentage of **1e** was higher than that of **1a**;[16] since we have proven that no isomerization of **1e** into **1a** takes place, either with **1e** alone in refluxing toluene or by treating **1e** with the anion of **1** in refluxing acetonitrile, it may be thought that the isomer ratios reflect the relative nucleophilicity of the different nitrogens of **1** (kinetic rather than thermodynamic control). In the case of **2**, the methylation under any of the above conditions gave curiously the 6-methyl derivative (**2c**) as the major product and **2e** and **2a** in small amounts. Treatment of **3** with an excess of dimethyl sulfate furnished a 25% yield of **3e**, a 17% of **3a**, a 5% of **3b**, and even smaller amounts of **3c**, whereas with cold methyl fluorosulfonate both **3a** and **3e** were isolated in 15–20% yields, the remaining isomers being present in the reaction mixture in very minute amounts; assignment of structures **3b** and **3c** was carried out by comparison of their spectra with those of **1b** and **2c** (see Table I).

In summary, the methylation of **1a–3a** under basic conditions takes place exclusively on N-1 (to afford **1–3a**) and N-2 (to give ylide-like or betaine-like compounds **1–3e**). In the absence of base, **1e–3e** give complex mixtures that also contain such betaines, sometimes as the predominant methylation products.

## Experimental Section

**General Methods and Starting Materials.** Melting points were determined on a Büchi apparatus and are uncorrected. The NMR spectra were obtained on a Varian XL-200 FT spectrometer (200 MHz for $^1H$, 50.3 MHz for $^{13}C$, and 20.3 MHz for $^{15}N$); chemical shifts are given in ppm with respect to internal $Me_4Si$ ($^1H$ and $^{13}C$) or external concentrated $H^{15}NO_3$, and $J$ values are in hertz; $^{13}C$ off-resonance spectra were often obtained, the reported assignments being in agreement with the observed multiplicities; for the nonroutine NMR techniques used in this work, see the corresponding footnotes in this section. The IR spectra were recorded in KBr on a Perkin-Elmer 681 instrument; only the most significant absorptions (in $cm^{-1}$) are indicated. Mass spectra were obtained on a Hewlett-Packard 5930 (EI method) or Hewlett-Packard 5890 (Cl method) spectrometers. UV spectra were recorded on a Perkin-Elmer Lambda 5 spectrophotometer; only the maxima are given (in nm). Elemental analyses were performed at the Departamento de Química Bioorgánica, C.S.I.C., Barcelona, Spain.

Meldrum's acid (**4**) was readily prepared according to ref 17. For the synthesis of 2-aminoimidazolium sulfate and 2-amino-1-methylimidazole hydrochloride, see ref 18 and 8a. 3(5)-Aminopyrazole and 3-amino-1-methylpyrazole were obtained from 2-chloroacrylonitrile and hydrazine or methylhydrazine, respectively.[19] Labeled $NaNO_2$ (≥95% in $^{15}N$), either from the Comissariat à l'Energie Atomique (Gif-sur-Yvette, France) or from

(13) Preparation of **3d** has been attempted without success: diazo-*s*-triazole and 1,1-dimethoxyethene react in acetone to afford 1,4-dihydro-4,4-dimethoxy-1,2,4-triazolo[5,1-*c*][1,2,4]triazine (besides its 3,4-*c* isomer) in good yield, but elimination of one molecule of methanol from this compound turned out to be more difficult than in the pyrazole and imidazole counterparts, and under more extreme reaction conditions only rearranged products[5b] were obtained. There are precedents of the formation of very stable covalent hydrates (and solvates) in related triazolotriazine systems (see, e.g., ref 4b and Rusinov, V. L.; Petrov, A. Yu.; Postovskii, I. Ya. *Khim. Geterotsikl. Soedin.* **1980**, *16*, 1283). For a review on covalent hydration, see: Albert, A. *Adv. Heterocycl. Chem.* **1976**, *20*, 117.

(14) As expected, no NOE was observed on H-3 by irradiation of the methyl group of **1a–3a**.

(15) (a) Levy, G. C.; Lichter, R. L. *Nitrogen-15 NMR Spectroscopy*; Wiley: New York, 1979. (b) Martin, G. J.; Martin, M. L.; Gouesnard, J.-P. *$^{15}$N-NMR Spectroscopy*; Springer-Verlag: Berlin, 1981. (c) Witanowski, M.; Stefaniak, L.; Webb, G. A. In *Annual Reports on NMR Spectroscopy*; Academic Press: London, 1986; Vol. 18.

(16) For a related case, see: Theuer, W. J.; Moore, J. A. *J. Org. Chem.* **1967**, *32*, 1602 and references therein.

(17) Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426.

(18) Storey, B. T.; Sullivan, W. W.; Moyer, C. L. *J. Org. Chem.* **1964**, *29*, 3118.

(19) Ege, G.; Arnold, P. *Synthesis* **1976**, 52.

the Junta de Energía Nuclear (Madrid, Spain) was utilized. The remaining starting materials also were commercial products.

**Preparation of 5 and Related Compounds.** Sodium nitrite (1.97 g, 28.5 mmol) in a small volume of water was added dropwise to a stirred solution of 3.46 g of 2-aminoimidazolium sulfate (13.1 mmol, i.e. 26.2 mmol of amine) in ca. 30 mL of 2 M $H_2SO_4$ cooled to −5 °C. After buffering the resulting solution to pH 6, it was added dropwise to a stirred, saturated aqueous solution of **4** (3.77 g, 26.2 mmol) maintained at 0 °C. The precipitate that appeared was filtered off, washed with cold water, and dried to afford chromatographically pure hydrazone **5** (5.20 g, 83%). Analogues of **5** were prepared in the same way in similar yields (70–90%).

Isopropylidene 2-imidazolylhydrazonomalonate (**5**): dec ca. 260 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 1.60 (s, 6 H), 7.20 (s, 2 H); IR 1740, 1680. Isopropylidene 3(5)-pyrazolylhydrazonomalonate: dec ≥250 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 1.66 (s, 6 H), 6.38 (d, $J$ = 2.4, 1 H), 7.75 (d, $J$ = 2.4, 1 H); IR 1735, 1695. Isopropylidene 1,2,4-triazol-3-ylhydrazonomalonate: mp 200–202 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 1.70 (s, 6 H), 8.50 (s, 1 H); IR 1730, 1695. Isopropylidene 1-methylimidazol-2-ylhydrazonomalonate: mp 121–122 °C; $^1$H NMR ($CDCl_3$) δ 1.70 (s, 6 H), 3.85 (s, 3 H), 6.70 (d, $J$ = 2.0, 1 H), 6.85 (d, $J$ = 2.0, 1 H); IR 1750, 1690. Isopropylidene 1-methylpyrazol-3-ylhydrazonomalonate: mp 173–176 °C dec; $^1$H NMR ($Me_2SO$-$d_6$) δ 1.70 (s, 6 H), 3.80 (s, 3 H), 6.32 (d, $J$ = 2.0, 1 H), 7.70 (d, $J$ = 2.0, 1 H); IR 1745, 1685. Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.20. Found: C, 47.46; H, 4.78; N, 21.92.

**Azolotriazinones 1 (and 6), 2 (and 7), 3, and 1b.** The hydrazones just described (2.0 g) were heated in refluxing AcOH (200 mL) for 24 h. Elimination of the solvent in vacuo afforded solids which were washed with cold water and dried into a vacuum desiccator to yield 1.2 g (99%) of **1**, 1.3 g (90%) of **7**, 1.0 g (87%) of **3**, and 1.2 g (98%) of **1b**, respectively. (When heating of **5** was stopped after half an hour, **6** was mainly obtained.) Heating of **7** in refluxing pyridine for 48 h, followed by elimination of the solvent, gave **2** in 95% yield. On the other hand, only decomposition products—mainly 3-acetamido-1-methylpyrazole—were obtained instead of **2c** when isopropylidene 1-methylpyrazol-3-ylhydrazonomalonate was submitted to the same cyclization conditions.

**1**: mp 265 °C dec; $^1$H NMR ($Me_2SO$-$d_6$) δ 7.39 (d, $J$ = 2.0, H-7), 7.60 (s, H-3), 7.67 (d, $J$ = 2.0, H-6); $^{13}$C NMR ($Me_2SO$-$d_6$) δ 107.8 (C-6), 128.1 (C-3), 130.0 (C-7), 144.2 (C-8a), 151.1 (C-4);[20] IR 1695; MS, $m/z$ 136 ($M^+$). Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.26; H, 2.98; N, 41.28.

**6**: dec ca. 250 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 7.62 (d, $J$ = 2.0, H-7), 7.81 (d, $J$ = 2.0, H-6); IR 1720–1690.

**2**: mp >300 °C (lit.[4a] mp 344–345 °C); $^1$H NMR ($Me_2SO$-$d_6$) δ 6.28 (d, $J$ = 2.1, H-8), 7.50 (s, H-3), 8.00 (d, $J$ = 2.1, H-7); $^{13}$C NMR ($Me_2SO$-$d_6$) δ 87.9 (C-8), 128.2 (C-3), 142.9 (C-8a), 144.8 (C-7), 149.6 (C-4); MS, $m/z$ 136 ($M^+$).

**7**: mp >300 °C; $^1$H NMR δ 6.52 (d, $J$ = 2.0, H-8), 8.15 (d, $J$ = 2.0, H-7); IR 1730–1690.

**3**: mp 236–238 °C (lit.[2] mp 236–240 °C); $^1$H NMR ($Me_2SO$-$d_6$) δ 7.80 (s, H-3), 8.35 (s, H-7); $^{13}$C NMR ($Me_2SO$-$d_6$) δ 132.7 (C-3), 150.0 (C-4), 151.5 (C-8a), 153.4 (C-7);[21] IR 1690; MS, $m/z$ 137 ($M^+$).

**1b**: mp 280–283 °C; $^1$H and $^{13}$C NMR, see Table I; IR 1670; MS, $m/z$ 150. Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: C, 48.05; H, 3.95; N, 37.10.

**Methylation of the Anions of 1, 2, and 3.** Solutions of **1–3** (5 mmol) and KOH (5.5 mmol) in ca. 100 mL of methanol were stirred at room temperature with 7.5 mmol of methyl iodide for 30 h. The reaction mixtures were concentrated to dryness under reduced pressure and the residues were continuously extracted with chloroform. Elimination of the solvent gave solids (in yields between 67% and 85%), which were separated by "flash" chromatography[22] on silica gel with $CHCl_3$–MeOH 95:5 as the eluent to afford **1a** (290 mg, 39%) and then **1e** (245 mg, 32%), **2a** (285 mg, 38%) and then **2e** (ca. 285 mg, 38%), and **3a** (224 mg, 30%) and then **3e** (180 mg, 20%), respectively.

**1a**: mp 159–160 °C; IR 1700; MS, $m/z$ 150 ($M^+$). Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: 48.03; H, 4.01; N, 37.12.

**1e**: mp 247–250 °C dec; IR 1680; MS, $m/z$ 150 ($M^+$). Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: C, 47.90; H, 4.04; N, 37.10.

**2a**: mp 185–187 °C; IR 1700; MS, $m/z$ 150 ($M^+$). Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: C, 48.21; H, 3.97; N, 37.28.

**2e**: mp 180–183 °C; IR 1680; MS, $m/z$ 150 ($M^+$). Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: C, 47.69; H, 4.11; N, 36.97.

**3a**: mp 171–173 °C (lit.[2] mp 174 °C); IR 1710; MS, $m/z$ 151 ($M^+$); UV 299, 243.

**3e**: mp 211–214 °C (lit.[2] mp 207 °C); IR 1690; MS, $m/z$ 151 ($M^+$); UV 341, 254.

**Preparation of 2c** from isopropylidene 1-methylpyrazol-3-ylhydrazonomalonate. A mixture of powdered hydrazone (375 mg, 1.5 mmol) and silica gel was heated for 5 min at 185 °C in a sublimator, and then it was readily connected to the vacuum line (≤0.1 mmHg). The sublimate was purified by column chromatography on silica gel to afford 33 mg (14%) of 6-methylpyrazolo[5,1-$c$][1,2,4]triazin-4-one (**2c**) as a white-yellow solid: 213 °C dec; $^1$H and $^{13}$C NMR, see Table I; IR 1680; MS(Cl), $m/z$ 151 ($M + 1^+$). Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: C, 47.85; H, 3.90; N, 36.99.

From **2**. To a suspension of 200 mg (1.5 mmol) of **2** in 10 mL of anhydrous acetonitrile were added 189 mg (1.5 mmol) of freshly distilled dimethyl sulfate. The mixture was refluxed for 48 h, the solvent was eliminated in vacuo, and the residue was treated with cold aqueous $NaHCO_3$. Elimination of water in vacuo and purification of the residue by flash chromatography on silica gel gave 148 mg (66%) of **2c**.

**Isolation of 3b and 3c.** A mixture of 738 mg (3 mmol) of **3** and 5 mL of dimethyl sulfate was stirred at 70 °C for 1 h. It was then left to stand overnight. Most of the excess of dimethyl sulfate was separated and aqueous $NaHCO_3$ was added to the residue. Elimination of water in vacuo (without heating) and separation of the resulting mixture by flash chromatography afforded 138 mg (17%) of **3a**, 200 mg (25%) of **3e**, 37 mg (5%) of 8-methyl-1,2,4-triazolo[5,1-$c$][1,2,4]triazin-4-one (**3b**, mp 240–243 °C; $^1$H and $^{13}$C NMR, see Table I; IR 1700; MS, $m/z$ 151 ($M^+$). Anal. Calcd for $C_5H_5H_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.50; H, 3.10; N, 46.07), and ca. 10 mg (1–2%) of 6-methyl-1,2,4-triazolo[5,1-$c$][1,2,4]triazin-4-one (**3c**, mp 201–204 °C dec; $^1$H and $^{13}$C NMR, see Table I; IR 1695; MS, $m/z$ 151 ($M^+$). Anal. Calcd for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.47; H, 3.13; N, 46.14).

**Preparation of $^{15}$N-Labeled Compounds.** Partially labeled **5** (i.e. **5** + **5***) was prepared from 765 mg of 2-aminoimidazolium sulfate and a mixture of 250 mg (3.63 mmol) of $NaNO_2$ and 150 mg (2.14 mmol) of $Na^{15}NO_2$ (ca. 95% of $^{15}$N). Heating of **5** + **5*** in AcOH as above afforded **1** + **1***, which was methylated according to the method already described.

**1***: $^1$H NMR ($Me_2SO$-$d_6$) δ 7.35 (d, $J$ = 1.6, H-7), 7.50 (d, $J$(H–N*) = 13.9, H-3), 7.60 (d, $J$ = 1.6, H-6).

**Acknowledgment.** We are indebted to the Ministerio de Educación y Ciencia for fellowships (E.F., INAPE, 1978–81; J.F., FPI, 1982–86) and to the Fundació A. Pedro i Pons for a fellowship to J.F. (1987). Nonroutine NMR experiments were carried out by Dr. M. Feliz. J.V. thanks

(20) The assignment of the quaternary carbons was performed from the undecoupled spectrum: the signal at δ 151.1 appears as a doublet with $^2J$ = 9.9 Hz and that at δ 144.2 as a doublet of doublets with apparent $^3J$ values of 12.1 and 7.0 Hz. The remaining carbon atoms also show the expected splittings: C-7 as a doublet of doublets (192.6 and 10.0 Hz), C-3 as a doublet ($^1J$ = 193.6 Hz), and C-6 as a doublet of doublets (200.4 and 15.7 Hz). Such assignments correlate quite well with those carried out for **2** and **3** and for their respective methylation products.

(21) The assignment of C-4 and C-8a was corroborated by a 2D-NMR experiment, using the HETCOR pulse sequence and adjusting the delays to correlate the two- and three-bond coupled $^1$H and $^{13}$C nuclei. (For leading references, see: (a) Bax, A. *Two-Dimensional NMR in Liquids*; Reidel: Dordrecht, 1982. (b) Benn, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 350.) It turns out that the proton at δ 7.80 (H-3) is related to the quaternary carbon atom at δ 150.0 (C-4, therefore), whereas the proton at δ 8.35 (H-7) shows a cross peak with the quaternary carbon at δ 151.5 (C-8a, therefore). For the sake of comparison, see compound **13** in ref 6b.

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B. Vallverdú for the p$K_a$ measurement of imidazole-2-diazonium cation (starting from 2-aminoimidazole hydrochloride instead of its sulfate), which corroborated the formerly reported value.

**Registry No.** 1, 59214-43-6; **1a**, 112298-51-8; **1b**, 112298-48-3; **1e**, 112298-52-9; **2**, 112298-50-7; **2a**, 112298-53-0; **2c**, 112298-56-3; **2e**, 112298-54-1; **3**, 57351-74-3; **3a**, 59105-03-2; **3b**, 112298-57-4; **3c**, 112298-58-5; **3e**, 112298-55-2; **4**, 2033-24-1; **5**, 112298-42-7; **6**, 112298-49-4; **7**, 112298-47-2; isopropylidene 3(5)-pyrazolylhydrazonomalonate, 112298-43-8; isopropylidene 1,2,4-triazol-3-ylhydrazonomalonate, 112298-44-9; isopropylidene 1-methylimidazol-2-ylhydrazonomalonate, 112298-45-0; isopropylidene 1-methylpyrazol-3-ylhydrazonomalonate, 112298-46-1; 2-aminoimidazolium sulfate, 36946-29-9; 3(5)-aminopyrazole, 1820-80-0; 2-amino-1-methylimidazole hydrochloride, 1450-94-8; 3-amino-1-methylpyrazole, 1904-31-0.

**Supplementary Material Available:** $^1$H NMR, $^{13}$C NMR, and $^{15}$N NMR spectra of **1a** and **1e** labeled partially at N-2 (1 page). Ordering information is given on any current masthead page.

## Quinone Methide *p*-Hydroxybenzylation of 1,3-Diketones

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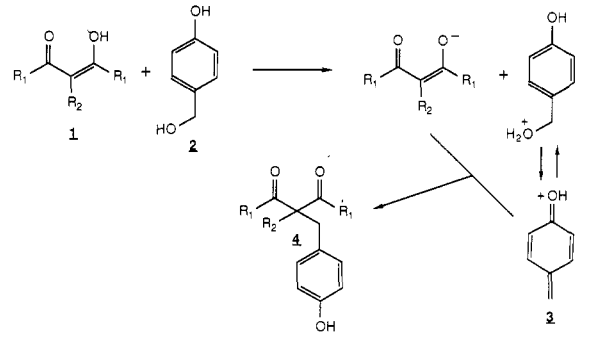
The Michael addition of 1,3-diketones to unsaturated compounds is well documented and has been extensively utilized in the preparation of natural products.[1] Quinone methides are conjugated homologues of vinyl ketones but are more reactive due to the additional driving force of aromatization after conjugate addition. The application of these highly conjugated intermediates to the formation of carbon–carbon bonds is limited by the stability of the quinone methide and the method for its generation.[2] Recently, the synthesis of delesserine has been achieved by the addition of 2-*O*-methylascorbic acid to the protonated methylene quinone derived from *p*-hydroxybenzyl alcohol.[3] Herein, we describe the application of this methodology to the C-2 benzylation of 1,3-diketones.

Treatment of cyclic and acyclic enolizable 1,3-diketones, **1**, with *p*-hydroxybenzyl alcohol, **2**, in water lead to carbon alkylation products, **3**.[4] These vinylogous acids are sufficiently acidic to facilitate generation of protonated quinone methides.[5] Consequently, the reaction proceeds by protonation of the benzylic alcohol, elimination of water to **4**, and finally addition of the conjugate base of **1** to yield **3**.[6] When ethyl acetoacetate or ethyl 2-oxocyclopentanecarboxylate was exposed to an aqueous solution of **2**, no addition product was observed.



| $R_1$ | $R_2$ | Yield (%) |
|---|---|---|
| $CH_3$ | H | 78 |
| $-CH_2-CH_2-$ | H | 18 |
| $-CH_2-CH_2-CH_2-$ | H | 22 |
| $-CH_2-C(CH_3)_2-CH_2-$ | H | 18 |
| $-CH_2-CH_2-$ | $CH_3$ | 97 |
| $-CH_2-CH_2-CH_2-$ | $CH_3$ | 73 |

### Experimental Section

**Typical Procedure. Preparation of 2-(4-Hydroxybenzyl)-2-methyl-1,3-cyclopentanedione.** To 2-methyl-1,3-cyclopentanedione (111 mg, 1.0 mmol) in water (3 mL) was added *p*-hydroxybenzyl alcohol (62 mg, 0.5 mmol), and the solution was stirred at 80 °C for 12 h. The reaction mixture was evaporated and the residue chromatographed (1:1 EtOAc/hexanes) to give 105 mg (97%) of 2-(4-hydroxybenzyl)-2-methyl-1,3-cyclopentanedione: mp 146–147 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.18 (s, 3 H), 1.8–2.8 (m, 4 H), 2.88 (s, 2 H), 5.8–6.2 (br s, 1 H), 6.6 (d, $J$ = 14.5 Hz, 2 H), 6.85 (d, $J$ = 14.5 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.7, 35.9, 42.5, 58.7, 115.5, 127.4, 130.8, 155.2, 218.6; IR ($CDCl_3$) $\nu$ 1730, 1619, 1522 cm$^{-1}$; MS (70 eV), $m/e$ (relative intensity) 218 (9.7), 107 (100), 77 (7.4). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.40; H, 6.5.

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(6) Treatment of an aqueous solution of 2-methyl-1,3-cyclopentanedione with benzyl alcohol gave no addition product. Thus, the *p*-hydroxy group is necessary for reaction. See also: ref 3.

## Thioanhydrides. 2. Synthesis of Phthalic Thiothionoanhydrides†

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Phthalic thioanhydride (**1**) has been a well-known compound since 1911,[1] but its unstable isomer, phthalic thionoanhydride (**2**), is the subject of only a single report.[2] The thione **2** readily isomerizes to **1**. Neither of the phthalic dithioanhydrides **4** or **5** has been reported previously, although both 1,8-naphthalic dithioanhydride and 1,8-naphthalic thiothionoanhydride have been made in these laboratories.[3] Phthalic thiothionoanhydride (**5**) has now been synthesized by the reaction of *tert*-butyl mer-

† For Part 1, see ref 3.

 