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A ^{13}C Study of Hydroxymethyl Derivatives of Five-Membered Ring Heterocycles

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The ^{13}C spectra of the hydroxymethyl derivatives of pyrrole, furan, 5,5-dimethylhydantoin, imidazole, thiophene, pyrazole, and phenol have been studied and assigned. The substituent parameters for the hydroxymethyl group in pyrrole, thiophene, furan, and imidazole were determined.

KEY WORDS ^{13}C NMR Substituent parameters Hydroxymethyl group Pyrrole Furan Imidazole 5,5-Dimethylhydantoin Thiophene

INTRODUCTION

Von Baeyer[1a] first studied the products from the reactions of phenols and aldehydes in 1872; since then, the mechanism and synthetic applications have been investigated thoroughly.[1b] It is now generally agreed that under basic conditions the initial step in the reaction of phenol with formaldehyde is the formation of the five possible mononuclear mono-, di- and trihydroxymethylphenols with CH_2OH groups in the *ortho* and/or *para* positions. A subsequent step is prepolymer formation, which involves condensation reactions between either (i) a hydroxymethyl group of one hydroxymethylphenol and a hydroxymethyl group of another hydroxymethylphenol to give a binuclear system with a dibenzyl ether linkage, or (ii) between a hydroxymethyl group of one hydroxymethylphenol and an unsubstituted *ortho* or *para* position of phenol (or of a hydroxymethylphenol) to give a methylene-bridged binuclear derivative.

Many heterocycles, such as pyrrole,[2] 5,5-dimethylhydantoin,[3,4] furan,[5] imidazole,[6] thiophene and pyrazole,[7] react with HCHO to yield hydroxymethyl derivatives. Some, such as thiophene[8] and furan,[9] even undergo further condensation reactions in acidic condition to give resins by a mechanism similar to that by which phenolic resins are formed. Hence, hydroxymethyl groups attached to these heterocycles may also condense with phenolic nuclei or with hydroxymethyl groups attached to phenol rings in the phenolic prepolymer mixture.[8] Information on the structure of such modified resins should be available from ^{13}C NMR spectroscopy.

This paper describes the assignments of the ^{13}C lines of the hydroxymethyl derivatives of heterocycles which were made in order to assist the assignments of the ^{13}C lines of the co-prepolymers. The heterocycles used were pyrrole, furan, 5,5-dimethylhydantoin, thiophene, pyrazole and imidazole.

There have been several reports on the ^{13}C chemical shifts of a variety of hydroxymethylphenols.[10–13] To the best of our knowledge, no comprehensive ^{13}C study of the hydroxymethyl derivatives of heterocyclic compounds has been reported previously, although the characterization of furfuryl alcohol oligomers by ^{13}C has been well studied.[14]

RESULTS AND DISCUSSION

The structures of the compounds studied are shown in Scheme 1. 1-Hydroxymethylpyrrole (**1**) was prepared according to the method described by Lung and Yu.[2] 2-Hydroxymethylpyrrole (**2**) was obtained by the reduction of 2-pyrrolealdehyde with sodium borohydride as reported by Silverstein *et al.*[15] 2,5-Bis(hydroxymethyl)pyrrole (**4**) was prepared by stirring a mixture of paraformaldehyde, pyrrole and catalytic amount of sodium hydroxide at room temperature for 3 days. This procedure gave a cleaner product than that obtained by other methods[2,16] which also required higher temperatures. 1,2-Bis(hydroxymethyl)pyrrole (**3**), previously unknown, was prepared by the reaction of 2-pyrrolealdehyde with HCHO, followed by reduction with sodium borohydride (Scheme 2). 1,2,5-Tris(hydroxymethyl)pyrrole (**5**), also previously unknown, was prepared in quantitative yield by stirring 2,5-bis(hydroxymethyl)pyrrole (**4**) with HCHO at room temperature. 3-Hydroxymethylthiophene (**18**) was prepared by the reduction of 3-thiophenecarbaldehyde with $LiAlH_4$ in THF. Compounds **8**,[4] **9**,[3] **12**,[17] **13**,[6] **14**,[6] **15**,[18] **16**,[6] **19**[19] and **20**[7] were prepared by literature methods. Compounds **6**, **7**, **10**, **11** and **17** were obtained from Aldrich.

The chemical shifts of the 20 hydroxymethyl derivatives are listed in Table 1. The reported chemical shifts of **7**,[14] **10**,[10,12] **11**[10,12] and **12**[10,12] are in good agreement with our results although small differences arise from solvent effects. The assignments for **1**, **4** and **5** are straightforward since the structures are symmetrical: C-3 and C-4 absorb at 105.6–108.8 ppm, which is close

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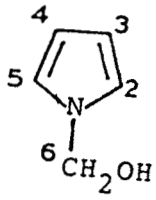

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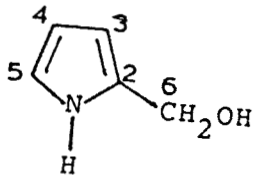

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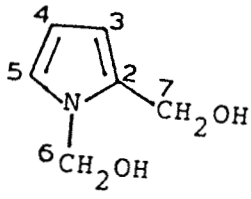

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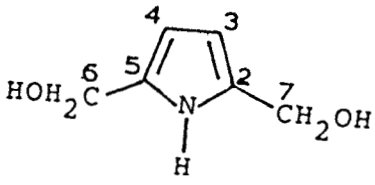

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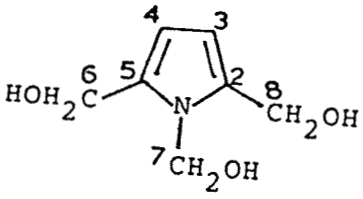

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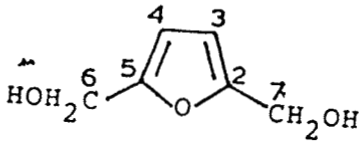

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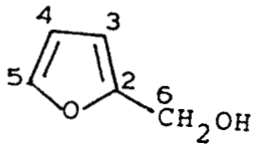

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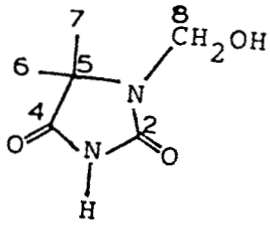

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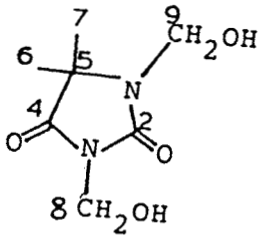

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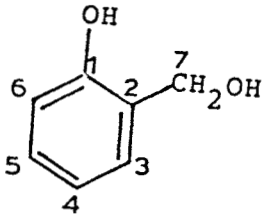

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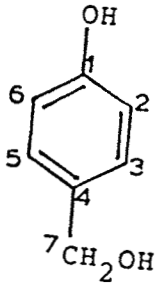

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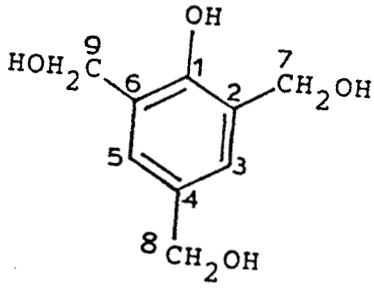

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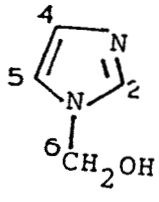

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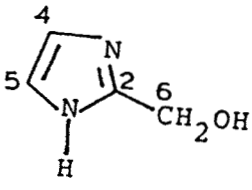

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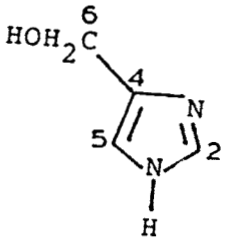

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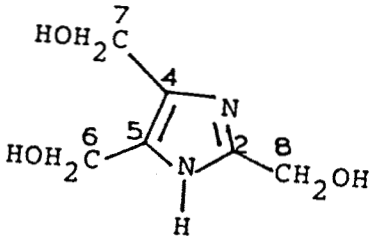

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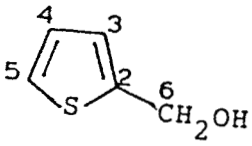

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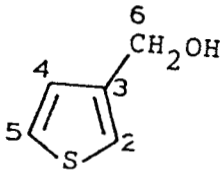

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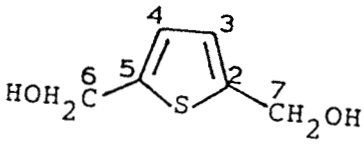

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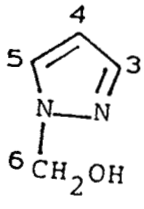

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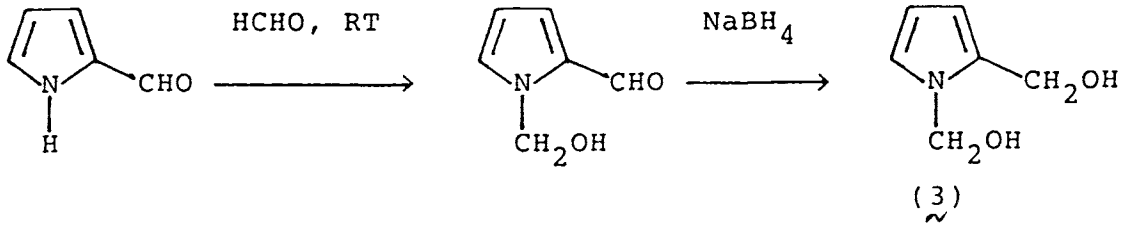
Scheme 1



Scheme 2

to that of the unsubstituted pyrrole (107.54 ppm). Carbons C-2 and C-5 of **1** give a signal at 120.70 ppm and **4** and **5** show peaks at 132.2–133.3 ppm for the same carbons. The hydroxymethyl groups of **1**, **4** and **5** give a signal at 55.0–56.6 ppm when attached to C-2 or C-5 and at 65.9–72.0 ppm when attached to the nitrogen. Based on the chemical shifts of **1**, **4**, **5** and unsubstituted pyrrole, the chemical shifts assignments of **2** and **3** are unambiguous.

In **8** and **9** the ^{13}C shifts are well separated, and the assignments are obvious except for the resonances of the two hydroxymethyl groups of **9**. However, C-8 should absorb at lower field than C-9 because it is subject to the electronic effects of two adjacent carbonyl groups, whereas C-9 is next to only one such group. Steric compression arguments lead to the same conclusion.

For **13** the assignments of C-2 and C-6 are easy. Carbon C-4 should absorb at lower field than C-5 since the former is adjacent to a pyridine-like nitrogen whereas the latter is next to a pyrrole-like nitrogen. Compounds **14** and **16** are symmetrical so there is no problem in assigning the lines. The C-2 and C-4 lines of **15** are distinguished with the help of the APT technique. The symmetrical structure of **19** makes the assignments of the lines unambiguous. The assignments of the lines of **18** and **20** were made by comparison with those of 3-methylthiophene[20] and 1-methylpyrazole,[21] respectively.

Chemical shifts of hydroxymethyl group: effect of heterocyclic rings

The chemical shift of CH_3OH is 49.3 ppm. Table 1 contains the shifts of eight CH_2OH groups attached to heterocyclic nitrogens, lying in the range 61.3–73.6 ppm. Within this range the shift depends on the type of nitrogen: highest field for amide-N (**8** and **9**), intermediate for pyrrole, in which additional $C—CH_2OH$ may decrease the shift (**1**, **3** and **5**), and lowest field for imidazole and pyrazole (**13** and **20**).

Table 1 also contains the shifts of 17 unique $C—CH_2OH$ groups, lying in the range 54.5–63.6 ppm. Within this range CH_2OH groups attached to pyrrole, furan and imidazole fall at the high-field end, those attached to thiophene are intermediate and those attached to phenol (especially at the *para* position) are

Table 1. Chemical shifts of hydroxymethyl derivatives of pyrrole, furan, 5,5-dimethylhydantoin, imidazole, thiophene, pyrazole and phenol[a,b]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
1	—	120.70	108.76	108.76	120.70	72.01	—	—	—
2	—	132.49	106.12	107.39	117.48	**56.66**	—	—	—
3	—	132.29	106.42	108.37	121.53	69.08	**54.87**	—	—
4	—	132.16	105.64	105.64	132.16	**56.56**	56.56	—	—
5	—	133.32	106.86	106.86	133.32	**55.05**	65.96	**55.05**	—
6	—	154.76	107.59	107.59	154.76	**55.88**	**55.88**	—	—
7	—	155.82	107.44	110.79	142.42	**56.29**	—	—	—
8	—	155.64	—	177.91	58.46	24.88	24.88	61.29	—
9	—	154.00	—	176.01	60.48	23.07	23.07	62.46[c]	60.98[c]
10	154.34	128.58	127.52	118.84	127.49	114.71	**58.50**	—	—
11	156.40	115.03	128.31	132.92	128.31	115.03	**63.07**	—	—
12	151.50	128.06	125.47	132.83	125.47	128.06	**60.16**	**63.63**	**60.16**
13	—	137.22	—	128.59	119.28	69.57	—	—	—
14	—	148.23	—	121.48	121.48	**56.85**	—	—	—
15	—	134.87[c]	—	134.71[c]	117.84	**55.88**	—	—	—
16	—	146.63	—	132.25	132.25	**54.56**	**54.56**	**56.90**	—
17	—	146.38	125.38[c]	127.37	125.13[c]	**59.29**	—	—	—
18	—	121.23	144.14	127.33	126.16	**59.48**	—	—	—
19	—	145.41	124.06	124.06	145.41	**58.80**	**58.80**	—	—
20	—	—	139.31	106.03	129.62	73.59	—	—	—

[a] Solvent, DMSO-d_6.
[b] Underlined values correspond to $N—\underline{C}H_2OH$; values in bold correspond to $C—\underline{C}H_2OH$.
[c] Assignments may be reversed.

Table 2. Effects of hydroxymethyl group substitutions on ring carbon shifts[a]

Ring system	Compound	CH_2OH position	C-2	C-3	C-4	C-5
Pyrrole	**1**	1-	+3.08	+1.22	+1.22	+3.08
Pyrrole	**2**	2-	+14.87	−1.42	−0.15	−0.14
Pyrrole	**3**	1,2-	+14.67	−1.12	+0.83	+3.91
Pyrrole	**4**	2,5-	+14.54	−1.90	−1.90	+14.54
Pyrrole	**5**	1,2,5-	+15.70	−0.68	−0.68	+15.70
Furan	**6**	2,5-	+12.00	−2.00	−2.00	+12.00
Furan	**7**	2-	+13.06	−2.15	+1.20	−0.34
Imidazole	**13**	1-	+1.76	—	+6.61	−2.70
Imidazole	**14**	2-	+12.77	—	−0.50	−0.50
Imidazole	**15**	4-	−0.59	—	+12.73	−4.14
Imidazole	**16**	2,4,5-	+11.17	—	+10.27	+10.27
Thiophene	**17**	2-	+20.91	−1.46	+0.53	−0.34
Thiophene	**18**	3-	−4.24	+17.30	+0.49	+0.69
Thiophene	**19**	2,5-	+19.94	−2.78	−2.78	+19.94
Pyrazole	**20**	1-	—	+6.62	+2.00	−3.07

[a] The chemical shifts of pyrrole in DMSO-d_6 are at 117.62 and 107.54 ppm, furan at 142.76 and 109.59 ppm, imidazole at 121.98 and 135.46 ppm, thiophene at 126.84 and 125.47 ppm and pyrazole at 132.69 and 104.03 ppm.

at the low-field end. There is no simple relationship between these shifts and the σ constants for the heterocyclic rings to which they are attached.

Effect of hydroxymethyl group substitution on ring carbon shifts

Substituent effects of the hydroxymethyl group(s) on pyrrole, furan, thiophene, imidazole and pyrazole ring carbon chemical shifts were determined and are listed in Table 2. For example, the substituent effects on pyrrole of a hydroxymethyl group at the N-1 and C-2 positions were calculated by comparing **1** and **2**, respectively, with the chemical shifts of unsubstituted pyrrole.

Ring carbon atoms attached directly to a CH_2OH group are subjected to a downfield shift of 10.3–20.9 ppm (17 examples). Within this range, thiophene is affected most, pyrrole is intermediate and furan and imidazole are least affected.

The other ring carbon atoms are much less affected, and shifts of -3.1 to $+6.6$ ppm are found. The carbons α to the CH_2OH substituents show the greatest shifts, and the shifts decrease as the distances between the carbons (β-, β'- and α'-carbons) and the CH_2OH group increase. This indicates that the effect is mostly inductive.

EXPERIMENTAL

^{13}C NMR measurement

Carbon-13 NMR spectra were obtained on a Varian XL-200 spectrometer operating at 50 MHz with DMSO-d_6 as the solvent at ambient temperature. Sample concentrations were approximately 15%. The 90° pulse widths were 3.6 μs and there was no pulse delay. The acquisition time was 0.970 s. DMSO-d_6 was used for lock, and its carbon peak at 39.5 ppm was used as the reference.

Reagent-grade model compounds **6**, **7**, **10**, **11** and **17** were purchased and used without further purification. The following were prepared by the literature methods indicated: 1-hydroxymethylpyrrole, b.p. 45–50 °C/1.5 mmHg (lit.,[22] b.p. 45.5–51 °C/1.5 mmHg); 2-hydroxymethylpyrrole, b.p. 75–79 °C/1.5 mmHg (lit.,[15] b.p. 81–83 °C/2 mmHg); 1-hydroxymethyl-5,5-dimethylhydantoin, m.p. 97–101 °C (lit.,[23] m.p. 110–117 °C); 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin, m.p. 86–88 °C; 2,4,6-tris(hydroxymethyl)phenol, m.p. 73–75 °C (lit.,[17] m.p. 74–75 °C); 1-hydroxymethylimidazole (picrate), m.p. 202 °C (lit.,[6] m.p. 202–203 °C); 2-hydroxymethylimidazole (hydrochloride), m.p. 112 °C (lit.,[24] m.p. 111–113 °C); 4-hydroxymethylimidazole, m.p. 90–91 °C (lit.,[25] m.p. 89–90 °C); 2,4,5-tris(hydroxymethyl)imidazole, m.p. 158 °C (lit.,[6] m.p. 158–159 °C); 2,5-bis(hydroxymethyl)thiophene, b.p. 174–178 °C/0.6 mmHg (lit.,[19] b.p. 162–166 °C/0.25 mmHg); 1-hydroxymethylpyrazole, m.p. 88 °C (lit.,[26] m.p. 89–90 °C).

Preparation of 1,2-bis(hydroxymethyl)pyrrole (3)

A mixture of 2-pyrrolealdehyde (0.2 g, 0.021 mol) and 37% HCHO solution (1.7 g, 0.021 mol) was heated on a steam-bath in a 10 ml round-bottomed flask for 3 h. Water was removed from the solution under reduced pressure. The crude 1-hydroxymethyl-2-pyrrolealdehyde was not purified because it is unstable and decomposes into 2-pyrrolealdehyde at room temperature. The compound decomposed on distillation. The ^{13}C NMR spectrum of the crude mixture showed that *ca* 80% of the 2-pyrrolealdehyde was converted into 1-hydroxymethyl-2-pyrrolealdehyde. ^1H NMR ($CDCl_3$), δ 9.44 (1H, s), 7.08 (3H, m), 6.23 (1H, t), 5.43 (2H, d); ^{13}C NMR ($CDCl_3$), δ 72.43, 110.00, 126.67, 131.51, 131.78, 180.29. 1-Hydroxymethyl-2-pyrrolealdehyde (0.35 g, 2.8×10^{-3} mol) was dissolved in 6 ml of water in a 25 ml round-

bottomed flask. A solution of $NaBH_4$ (0.4 g) in 2 ml of water was added over a period of 10 min. After 1 h the solution was saturated with K_2CO_3 and extracted with diethyl ether (3 × 25 ml). The ethereal extracts were combined and the solvent was removed under reduced pressure. The crude product decomposed into 2-hydroxymethylpyrrole on passing through a SiO_2 column or on distillation. The ^{13}C spectrum shows that the product mixture contained both **3** and 2-hydroxymethylpyrrole. ^{13}C NMR for **3** (DMSO-d_6): δ 54.87, 69.08, 106.42, 108.37, 121.53, 132.29.

Preparation of 2,5-bis(hydroxymethyl)pyrrole (4)

A mixture of pyrrole (6.7 g, 0.1 mol), paraformaldehyde (6 g) and 1 M NaOH solution (0.1 ml) was stirred at room temperature for 3 h in a 25 ml round-bottomed flask. The white solid was poured into 50 ml of $CHCl_3$ and the suspension was stirred and then filtered. The white solid was washed with $CHCl_3$ and then dried inside a vacuum desiccator. The yield was 5.89 g (46.4%). ^1H NMR (DMSO-d_6), δ 4.43 (4H, d), 4.82 (2H, t), 5.88 (2H, d), 10.62 (1H, br); ^{13}C NMR (DMSO-d_6), δ 56.56, 105.64, 132.16; IR (Nujol), 3000–3500, 1590, 1272, 1020 cm^{-1}; m.p. 115–116 °C (lit.,[27] m.p. 112–115 °C).

Preparation of 1,2,5-tris(hydroxymethyl)pyrrole (5)

A mixture of 2,5-bis(hydroxymethyl)pyrrole (0.51 g, 4×10^{-3} mol) and 37% HCHO solution (5×10^{-3} mol) was stirred at room temperature for 3 days and water was removed under reduced pressure. The crude product was purified using SiO_2–acetone. The yield was 0.41 g (65.4%); m.p. 99–100 °C; ^{13}C NMR (DMSO-d_6), δ 55.05, 65.96, 106.86, 133.32; ^1H NMR (DMSO-d_6), δ 4.46 (4H, d), 4.85 (2H, t), 5.33 (2H, d), 5.84 (2H, s); IR (Nujol), 3000–3500, 1571, 1366, 1298, 1249, 1193, 1115, 1030, 1002, 992, 963, 790, 764, 700 cm^{-1}.

Preparation of 3-hydroxymethylthiophene (18)

To a THF (20 ml) suspension of $LiAlH_4$ (0.38 g, 0.01 mol) in a 100 ml two-necked round-bottomed flask with a magnetic stirring bar, a gas inlet and a septum, a THF solution of 3-thiophenecarboxaldehyde (1.12 g, 0.01 mol) was added dropwise under argon atmosphere at 0 °C. Stirring was continued at room temperature for 3 h. The mixture was carefully poured over ice (50 g) and then CO_2 gas was bubbled through the solution until it was neutral. The solution was extracted with diethyl ether (3 × 100 ml). The ethereal extracts were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was distilled. The yield was 0.92 g (80.7%); b.p. 73 °C/6 mmHg (lit.,[28] b.p. 96 °C/15 mmHg); ^{13}C NMR (DMSO-d_6), δ 144.14, 127.33, 126.16, 121.23, 59.48; ^1H NMR (DMSO-d_6), δ 4.5 (2H, d), 5.12 (1H, t), 7.04 (1H, dd), 7.22 (1H, dd), 7.37 (1H, dd).

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